SYNTHESIS AND REACTIONS OF ENOL-LACTONES

A THESIS

PRESENTED FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

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by

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STATEMENT

This thesis contains no material previously submitted for a degree in any University, and to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference is made in the text.

P. J. BABIDGE

PUBLICATION

Part of the work described in this thesis has been published in the following paper:

Reactions of Stabilised Phosphoranes with Enol-lactones.
Babidge P.J., Massy-Westropp R.A.,
Aust. J. Chem., 1977, 30 , 1629.

ACKNOWLEDGEMENTS

I wish to sincerely thank Dr. R.A. Massy-Westropp for the advice and encouragement given to me during his supervision of this work. I would also like to thank those members of the Department who assisted me during this work.

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SUMMARY

Various enol-lactones have been synthesised from the reaction of five membered ring cyclic anhydrides and thio - ester stabilised phosphoranes and from the reaction of cyclic thioanhydrides and an ester stabilised phosphorane. Treatment of the thioester enol-lactones with Raney nickel failed to give the expected aldehyde product; the major product formed was that derived from complete loss of the thioester group. This reaction, however, proved to be an efficient general method for the synthesis of 5 - alkylidene furan - 2(5H) - ones.

Enol-lactones in which the double bond is conjugated with an ester group react with ethoxycarbonylmethylene triphenyl phosphorane under mild conditions to yield the normal Wittig product, derived from the lactone carbonyl group. When the double bond is conjugated with a ketone group, reaction occurs at both carbonyl groups. Factors affecting reactivity are discussed.

The absolute configuration of 2 - Methyl - N [1' - (1" - oxo - 3 - phenylprop - 2 - enyl) pyrrolidin - 2" -yl] butanamide (odorine), a bis-amide isolated from the leaf extracts of Aglaia odorata, has been determined by comparison with a synthetic sample. Two diastereoisomers of odorine and dihydroodorine of known stereochemistry were synthesised from L-proline.

Scoparenonediol, a sesquiterpene isolated from the leaf

extracts of Eremophila scoparia has been shown to be 8,11 - dihydroxyeudesm - 3-en-2-one from chemical and spectroscopic evidence and by conversion to the known compound epidihydropterocarpol (2,11 - dihydroxyeudesmane).

CHAPTER 1

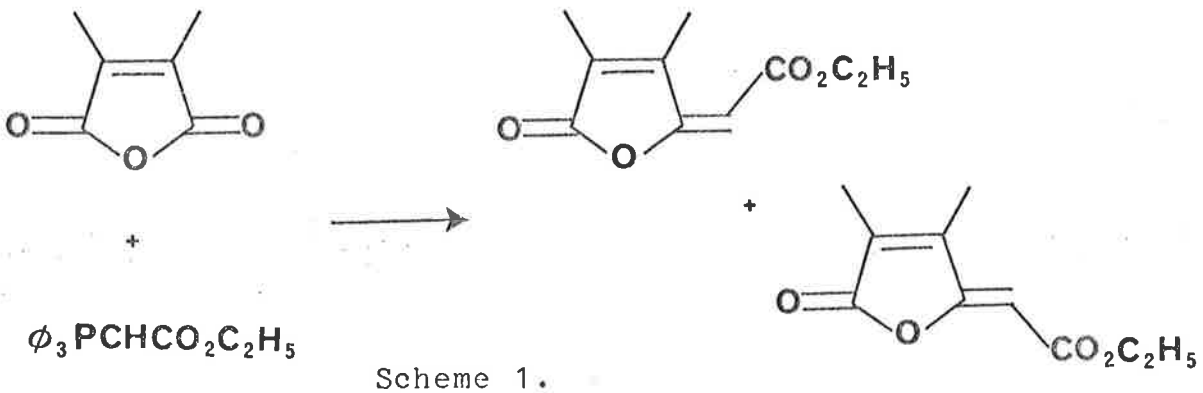
Synthesis and Reactions of Enol-lactones

INTRODUCTION

Many naturally occurring enol-lactones have been reported, for example the sesquiterpene freelingyne[1] and marine metabolites such as the fibrolides[2]. Much interest has been shown in this class of compound, firstly due to the fact that many possess antibiotic or antiviral activity, e.g. patulin[3], protoanemonin[4], tetrenolin[5], and penicillic acid[6], and secondly in their use as synthetic intermediates, e.g. their use as annelating agents[7], and for the synthesis of cyclopentenediones and cyclopentanediones[17].

Methods for the synthesis of five-membered enol-lactones include the cyclisation of cis-alk-2-en-4-ynoic acids[8], the cyclisation of γ-keto α,β-unsaturated acids or γ-keto acids with acetic anhydride[9,10], the reaction of Grignard reagents with anhydrides followed by dehydration[11,12] and the reaction of t-butoxyfuran with carbonyl compounds followed by treatment with acid[13].

Enol-lactones can also be synthesised from cyclic five-membered ring anhydrides and stabilised phosphoranes[14] (Scheme 1).

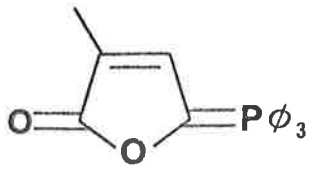


Scheme 1.

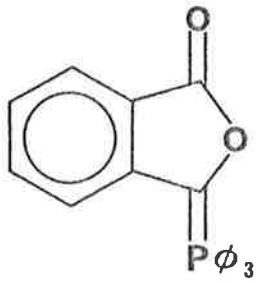
This is in contrast to the reaction of reactive phosphoranes and phosphonate anions with anhydrides, which gives no enol-lactone products[15]. Ester-stabilised phosphoranes generally give quite good yields of enol-lactones[14], however, keto-stabilised phosphoranes are not as satisfactory, with yields varying from near quantitative upon reaction with dimethylmaleic anhydride, to no recognisable product formed in the case of succinic anhydride[16]. The major product formed in the reaction of phthalic anhydride with various stabilised phosphoranes is the (E) isomer. The (E) isomer in these examples has been shown to be the kinetic product by isomerisation studies[14]. In contrast to the above results, the reaction of a substituted maleic anhydride with a keto stabilised phosphorane affords the thermodynamic mixture of products[14]. Similar results were obtained from the reaction of a substituted maleic anhydride with an ester stabilised phosphorane, although in this case the thermodynamic ratios of products are not known since no satisfactory method of isomerisation of the enol-lactones prepared using an ester stabilised phosphorane is available. Some preliminary investigation of the isomerisation of these compounds by the use of chlorosulphonic acid, however, indicates that the (Z) isomer is again the more stable[17]. Succinic anhydride and substituted succinic anhydrides form only the (E) enol-lactone upon treatment with an ester stabilised phosphorane. Here again these compounds have proven resistant to isomerisation so that little is known of the relative stability of the (E) and (Z) isomers.

Further information on the factors governing the formation of the (E) or (Z) isomer has been obtained in the present work from a comparison of the isomer ratios of thioenol-lactones, formed from thioanhydrides and a stabilised phosphorane, with those of the corresponding oxygen analogues.

To extend the utility of compounds of the type shown in Scheme 1 as synthetic intermediates, a greater variety of side-chains should easily be able to be added to the lactone ring. The Wittig method used for the synthesis of enol-lactones from cyclic anhydrides, while very convenient, has to date been limited to enol-lactones containing an ester or ketone group in the side chain[14]; compounds with an alkylidene side chain cannot be synthesised by this method. Enol-lactones can be formed by a Wittig reaction in the reverse sense, i.e. the treatment of a carbonyl compound with a phosphorane of the type (1)[18] or (2)[19];



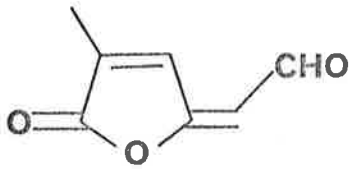
(1)



(2)

however this is not useful as a general method as these phosphoranes, especially (1), can be difficult to prepare and are also relatively unreactive. An enol-lactone of the type (3) would be useful since the side-chain could readily be extended or modified by manipulation of the alhehyde group. Attempts to synthesise an enol-lactone of this type,

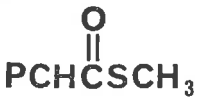
using the phosphorane (4), have been unsuccessful[16].



(3)

$\phi_3PCHCHO$

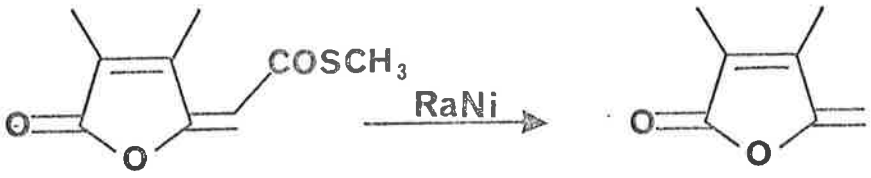
(4)



(5)

In the present study it was found that the reaction of anhydrides with a thioester-stabilised phosphorane, such as (5), generally gave good yields of the corresponding thioester enol-lactones. These compounds are potential precursors to the required aldehydes, since it should be possible to reduce the thioester group directly to an alhehyde by various means. The reducing agent investigated here was Raney nickel.

When the reductions were carried out, however, the results were quite unexpected. Aldehydes were produced in only a few examples, and then only as minor products. The major product generally formed was that derived from complete loss of the thioester group, (Scheme 2).



(10) (42)

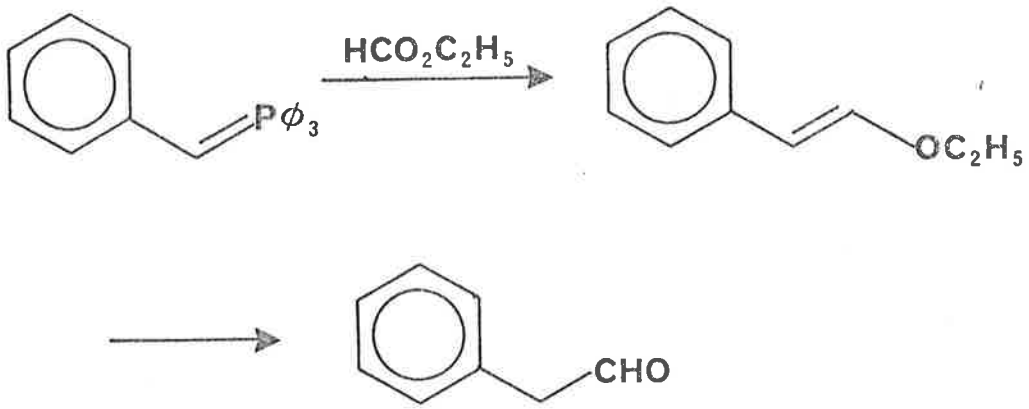
Scheme 2.

This then appears to be an efficient general route to compounds of the type (42), equivalent to the addition of a reactive phosphorane to an anhydride, a process that cannot be accomplished directly.

A number of 3,4 - dialkyl - 5 - alkylidenefuran -2(5H) - ones have been synthesised by the treatment of substituted maleic anhydrides with Grignard reagents followed by dehydration[12], which presumably led to the (Z) isomer. These compounds have found use as heavy metal sequestering agents, antioxidants and in flavoring and perfumery[12]. Alkylidenefuran -2(5H)-ones and alkylidenephthalides have been isolated from various natural sources. The chief odour and flavour principles of the celery plant for example are alkylidenephthalides and reduced alkylidenephthalides, and a characteristic component of butter flavour is 5-butylidene -2,3- dimethylfuran - 2(5H) - one[27]. The various general methods for the synthesis of enol-lactones already mentioned can also be used for the synthesis of alkylidenefuranones, however, the (Z) isomer is generally formed[27]. An advantage of the Wittig approach developed here is that both (E) and (Z) isomers can be produced. This could be important in for example the synthesis of some naturally occurring enol-lactones, which have the (E) stereochemistry for the side chain[27].

As an extension of this investigation of enol-lactones as synthetic intermediates, the reaction of these compounds with stabilised phosphoranes was investigated. The normal course of the reaction of a reactive phosphorane with esters or lactones is the formation of the acylated phosphonium salt[57,58] (Scheme 3).

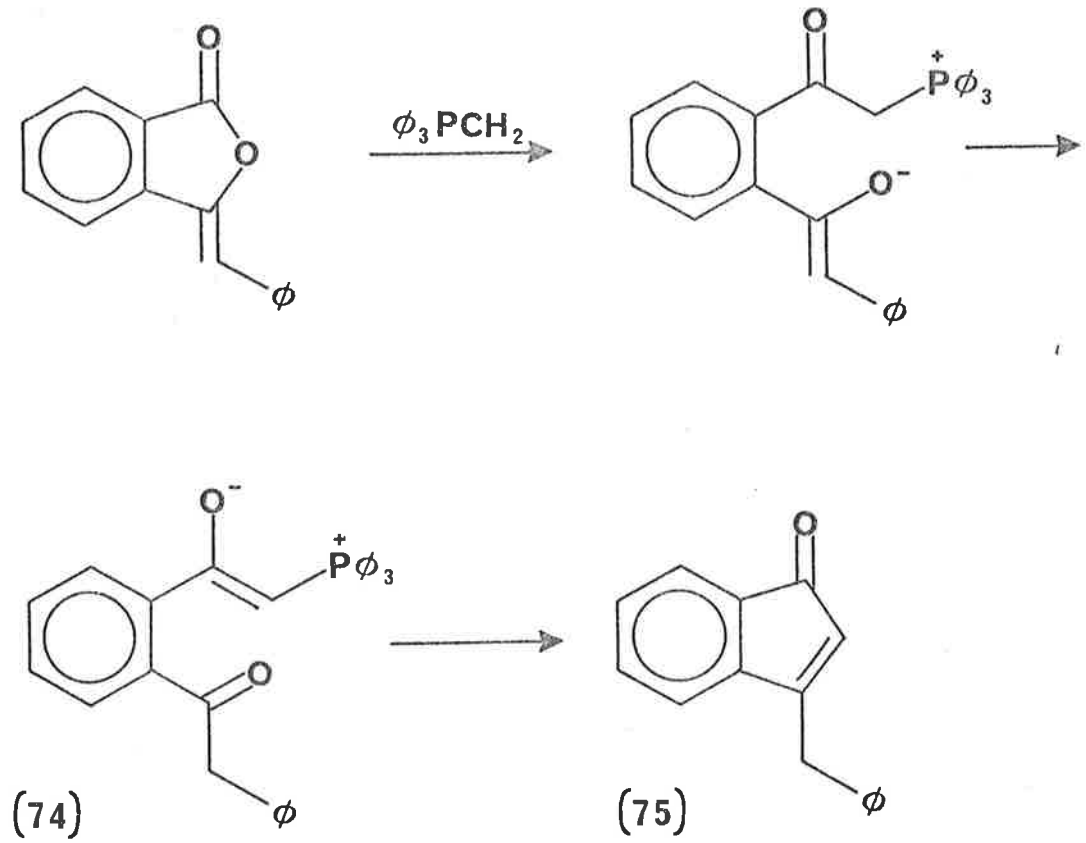
Scheme 3



Scheme 4

An exception to this generalisation are the formate esters; under suitable conditions these yield the product of a Wittig reaction rather than the acylated phosphorane [54], (Scheme 4). This is a special case, however, as these esters can be considered to contain both an ester and an aldehyde grouping.

Reactive phosphoranes have been found to form cyclic unsaturated ketones on reaction with enol-lactones[50], (Scheme 5). This occurs via the acylated phosphorane (74) which undergoes an intramolecular Wittig reation to give the product (75).



Scheme 5

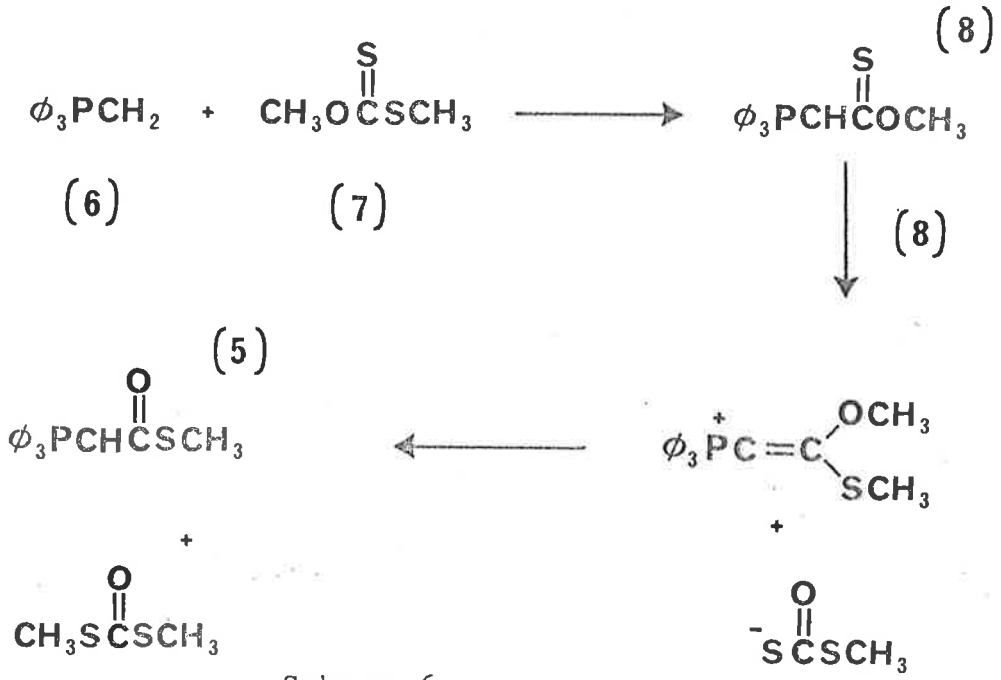
The results of the present study showed that enol-lactones in which the double bond is conjugated with an ester group react with stabilised phosphoranes to yield the normal Wittig product , derived from reaction at the lactone carbonyl group. In examples where the double bond was conjugated with a ketone group, reaction occurred at both carbonyl groups, depending on the nature of the enol-lactone. In all these compounds the carbonyl function is moderately reactive because of the delocalisation of the electron pairs on the lactone oxygen over a π system.

RESULTS AND DISCUSSION

1.1 The preparation of enol-lactones using (methylthio) carbonylmethylene-triphenylphosphorane (5)

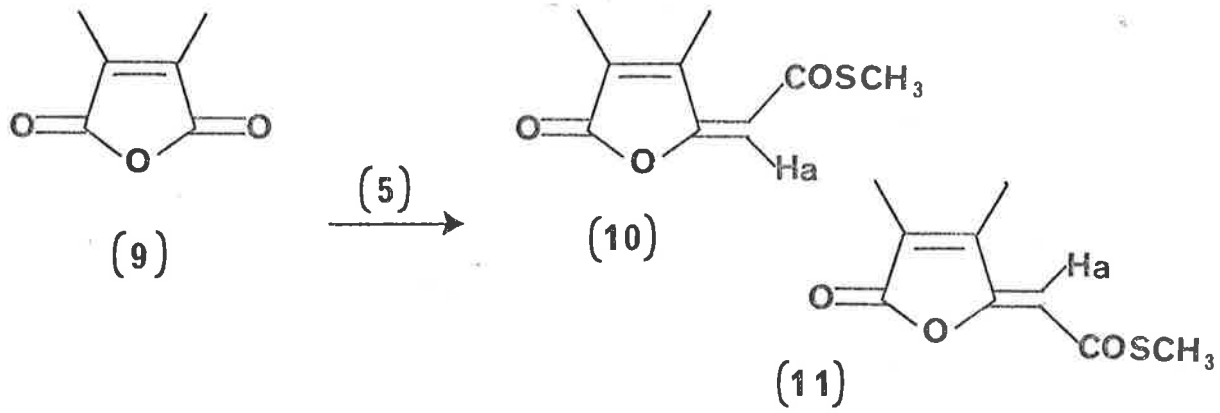
As mentioned in the introduction, enol-lactones can be prepared by the reaction of cyclic anhydrides with stabilised phosphoranes. In the present work the main interest was in enol-lactones prepared using thioester stabilised phorphoranes.

The phosphorane (5) was prepared by treating a solution of methylene - triphenylphosphorane (6) with two equivalents of methyl S-methyl xanthate (7). If only one equivalent of the xanthate is used in the reaction methyl(thiocarbonyl) methylene - triphenylphosphorane (8) is formed. It has been postulated that the second molecule of xanthate reacts with the initially formed phosphorane, as shown in Scheme 6, to form the (methylthio)carbonyl - methylenetriphenyl - phosphorane (5)[20].



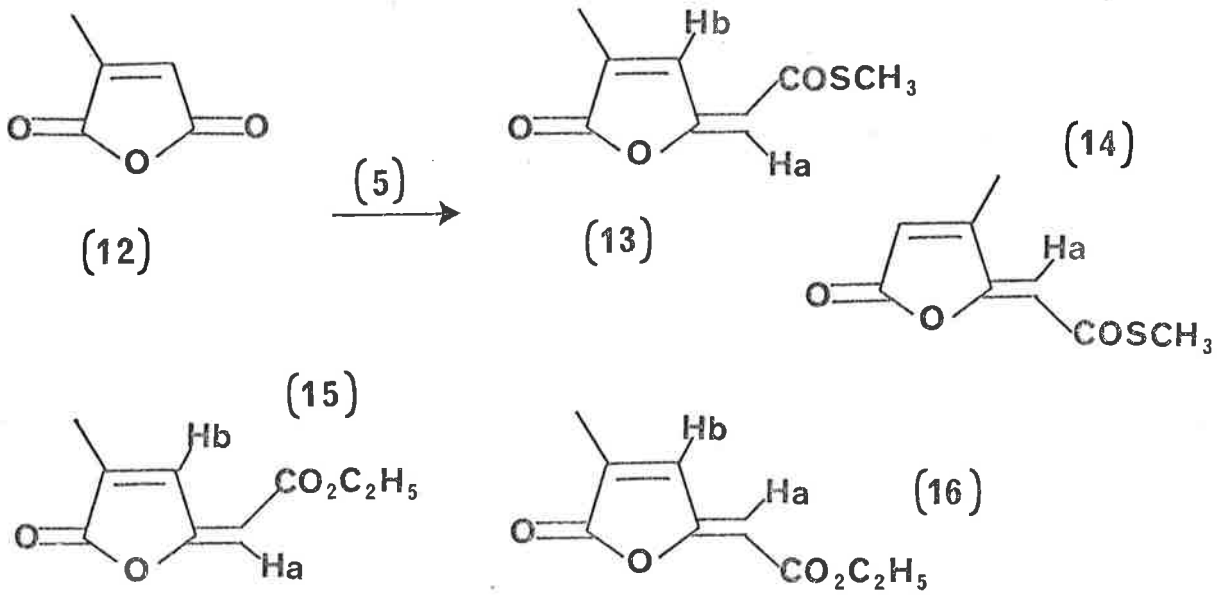
Scheme 6.

Treatment of dimethylmaleic anhydride (9) with the phosphorane (5) gave a good yield of the (E)(10) and (Z)(11) enol-lactones in a ratio of approximately 3:5. As might be expected, this ratio is similar to that of the enol-lactones obtained from the reaction of dimethylmaleic anhydride with ethoxycarbonylmethylene - triphenylphosphorane [14].



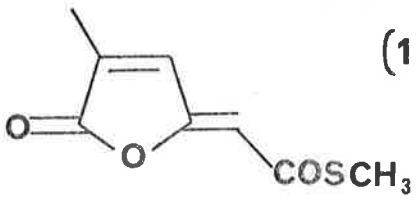
The stereochemistry of the products was assigned on the basis of the ^{1}H NMR spectra of the two compounds. It has previously been observed that the chemical shift of the proton H_a is at lower field in the (E) isomer than in the (Z) isomer, presumably due to the deshielding effect of the lactone oxygen[21,22]. On this basis, the isomer (10) with H_a at δ 6.22 was assigned (E) stereochemistry, and (11), with H_a at δ 5.72, (Z) stereochemistry. This assignment was further supported by the fact that the C3 methyl group in the isomer assigned as (E) absorbed at δ 2.27, compared with δ 2.08 in the (Z) isomer, presumably due to the deshielding effect of the thioester carbonyl group on these protons. The ^{13}C NMR spectra also showed the C3 methyl at lower field in the (E) isomer (δ 13.07) than in the (Z) isomer (δ 9.8), in agreement with expectations.

In an attempt to determine the effect that the C3 methyl group might have on the ratio of (E) and (Z) isomers formed in this type of reaction, the next example investigated was the treatment of citraconic anhydride (12) with the phosphorane (5). This reaction afforded the two products (13) and (14) in a ratio of about 18:1, which is clearly quite different to the results obtained with dimethylmaleic anhydride (9). The steric effect of the C3 methyl group is therefore very important in this reaction. The stereochemistry of the major product, arising from attack of the phosphorane at the less hindered carbonyl group, was assigned as (E) from a comparison of its ^1H NMR spectrum with the spectra of compounds (15)[14] and (16)[17].



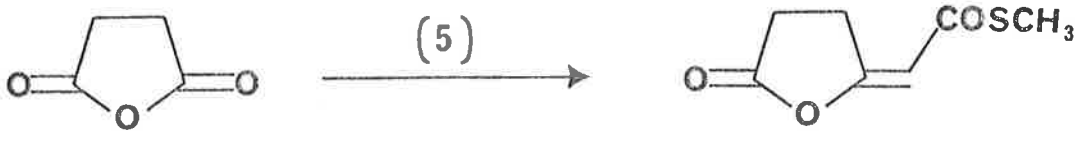
In compounds (15) and (16) H_b absorbs at δ 8.0 and δ 7.2 in the (E) and (Z) isomers respectively, this being due to the deshielding effect of the carbonyl group. In the product (13) obtained from this reaction H_b absorbs at δ 7.98, implying (E) stereochemistry. This is further supported by the chemical shift of H_a (δ 6.13), compared with δ 5.8 and δ 5.4 in (15) and (16) respectively. The minor product (14)

was assigned (Z) stereochemistry since the chemical shift of H_a (δ 5.73) agreed closely with that of the corresponding protons in (11) (δ 5.72) and (17) (δ 5.7). Later work in which the major product of this reaction (13) was isomerised to the (Z) isomer (17)[17] confirmed that the minor product (14) is derived from reaction at the more hindered carbonyl group, since the (Z) isomer (17) differed from the product (14).

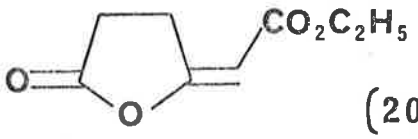


(17)

A further example of the reaction of the phosphorane (5) with an anhydride was one where the anhydride was fully saturated, namely succinic anhydride (18). The only product formed in this case was (19). The stereochemistry was assigned as (E) by comparison of its ^1H NMR spectrum with that of the known compound (20)[14].



(18) (19)



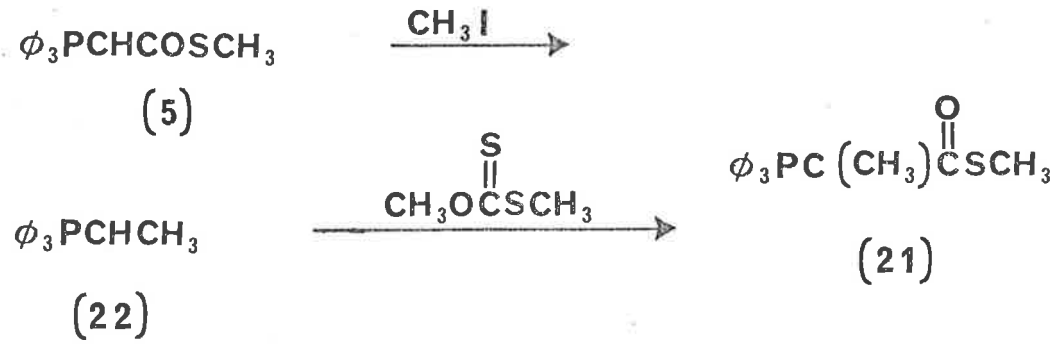
(20)

The chemical shifts of the C3 and C4 protons were virtually identical in (19) and (20), with the C3 protons being somewhat deshielded due to the adjacent carbonyl group. The olefinic protons also had similar chemical shifts and,

perhaps more importantly, almost identical coupling constants[14].

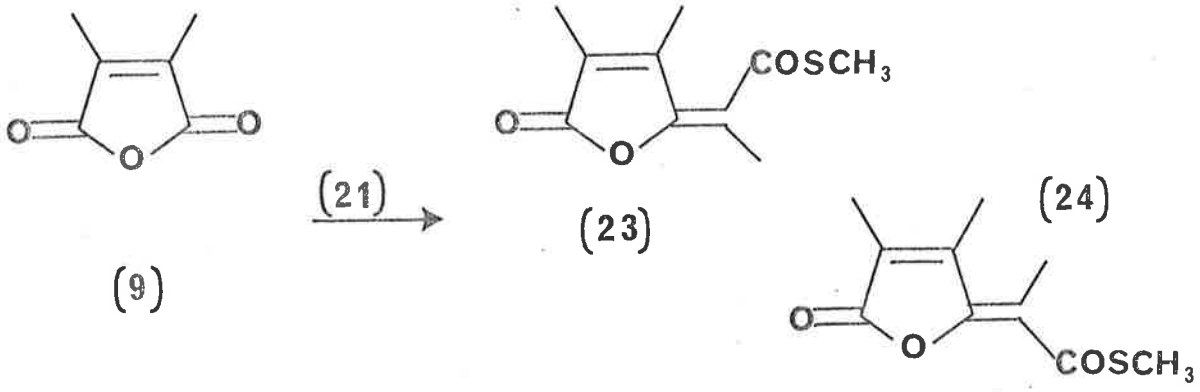
1.2 The preparation of enol-lactones using 1-(methylthio) carbonylethylidene- triphenylphosphorane (21)

Several enol-lactones were also prepared using the phosphorane (21) in order to provide a variety of substrates for the proposed Raney nickel reductions. The phosphorane (21) was prepared by two different methods, firstly by the alkylation of the phosphorane (5) with methyl iodide and secondly by treatment of ethylidene - triphenylphosphorane (22) with methyl S-methyl xanthate (7).



The latter proved to be the more satisfactory method, giving a 47% yield of the desired product after chromatography on alumina. Alkylation of the phosphorane (5) was complicated by the presence of starting material after work-up, which made the mixture very difficult to separate by chromatography. This problem could be overcome by carrying out the alkylation with a five-fold excess of methyl iodide, however yields were still low (ca. 36%).

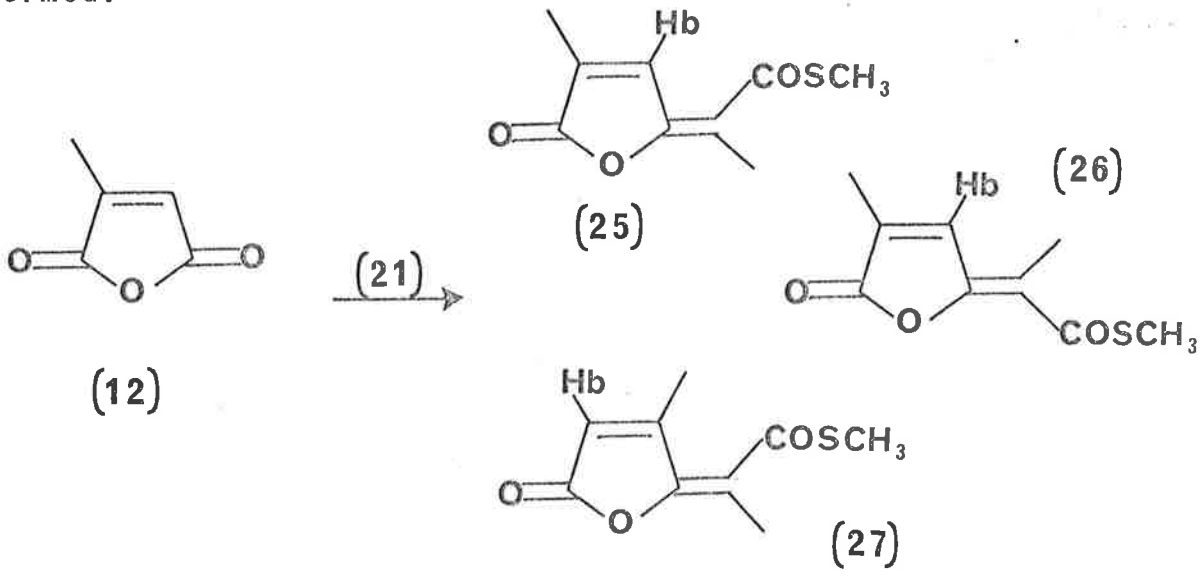
Treatment of dimethylmaleic anhydride (9) with the phosphorane (21) afforded a good yield of the two possible enol-lactones (23) and (24).



The assignment of the stereochemistry of these two isomers was more difficult than in previous cases due to the absence of characteristic olefinic proton absorbtions in their ^{1}H NMR spectra. The most significant difference in the ^{1}H NMR spectra of these two compounds was the chemical shift of the C3 methyl groups which were at δ 2.25 and δ 2.07. On this basis compound (24) with the methyl group at δ 2.25 would have been assigned (E) stereochemistry on the assumption that the methyl group is deshielded by the adjacent carbonyl, as was observed for the enol-lactone (10). The ^{13}C NMR spectra of these two compounds, however, indicated the opposite stereochemistry to that suggested by the ^{1}H NMR spectra. In this case compound (24), which had a chemical shift of δ 2.25 for the C3 methyl, had a ^{13}C shift for the same methyl of δ 14.06 while the other isomer, which had a shift of δ 2.07 for the C3 methyl, had a ^{13}C chemical shift of δ16.34 for this carbon. By analogy with the ^{13}C spectra of the enol-lactones (10) and (11) this suggested the (E) stereochemistry for the compound (23) with methyl carbon at δ16.34. The stereochemistry was

eventually assigned as (E) for (23) and (Z) for compound (24), as implied by the ^{13}C spectra, since this assignment was later supported by further reactions of these two isomers (p. 25,26).

A second example of the reaction of the phosphorane (21) with an anhydride was with citraconic anhydride (12). In this case three products were formed. The two major products were the (E) and (Z) olefins (25) and (26), arising from attack of the phosphorane at the less hindered carbonyl, which were formed in a ratio of about 4:1 respectively.This result differs from that obtained from the reaction of citraconic anhydride (12) with the phosphorane (5), where only the (E) isomer was produced. A small amount of the (E) olefin (27), arising from attack of the phosphorane at the more hindered carbonyl group, was also formed.

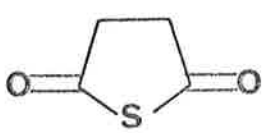


The stereochemical assignment for the two major products was quite straightforward and was based on the chemical shifts of the protons H_b. The compound with H_b at lower field should be the (E) isomer, since this proton should be

deshielded by the adjacent carbonyl group[14]. Compound (25), with H_b at δ 7.9, was therefore assigned as (E) and (26), with H_b at δ 7.52, as (Z). The minor product was assigned as arising from reaction at the more hindered carbonyl group because of the similarity of the shift of proton H_b to the corresponding proton in (14). The (E) stereochemistry was deduced indirectly from a later reaction of this compound (p. 28).

1.3 The preparation of enol-lactones from thioanhydrides and ethoxycarbonylmethylene - triphenylphosphorane (29)

In an attempt to obtain further information on the factors governing the formation of the (E) or (Z) enol-lactone from a cyclic anhydride, the reaction of thioanhydrides with a stabilised phosphorane was examined. Treatment of succinic thioanhydride (28)[23] with the phosphorane (29) gave a fair yield of the two possible enol-lactones (30) and (31) in a ratio of approximately 1:1, which is in marked contrast to the reaction of succinic anhydride (18) with either this phosphorane(29)[14] or with the phosphorane (5), where the (E) isomer is formed exclusively.



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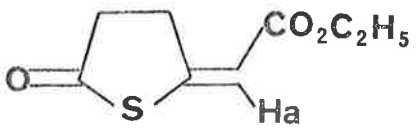

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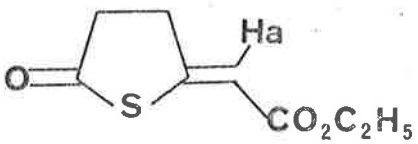
(31)

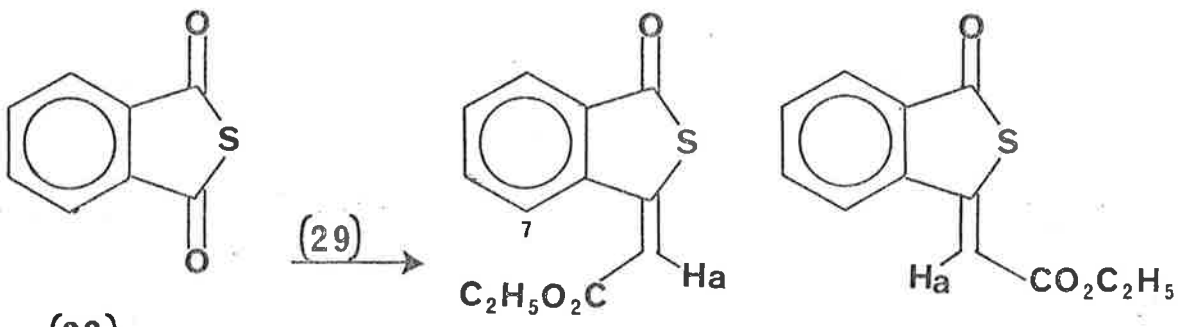


$\phi_3PCHCO_2C_2H_5$

(29)

The stereochemistry of the two isomers was again determined from their ^{1}H NMR spectra; the H3 protons in the (E) isomer absorb at lower field than the corresponding protons in the (Z) isomer due to deshielding by the adjacent carbonyl group. The large difference in chemical shifts of the protons H_a in the (E) and (Z) isomers observed in all previous cases was not observed here, confirming that this effect is indeed due to deshielding of this proton by the lactone oxygen. There was, however, a difference in the coupling constants of the two protons H_a; the (E) isomer had a coupling constant of 2.5Hz while the (Z) isomer had a coupling constant of 1Hz for this proton, further confirming the assigned stereochemistry[24].

The reaction of phthalic thioanhydride (32) with the phosphorane (29) provided another example where there might be different factors affecting the sterochemistry of the products. The two possible isomers (33) and (34) in the ratio 1:6 were obtained in good yield. This result once again differs significantly from those obtained from the reaction of phthalic anhydride with various stabilised phosphoranes, where the major product was always the (E) isomer[14].

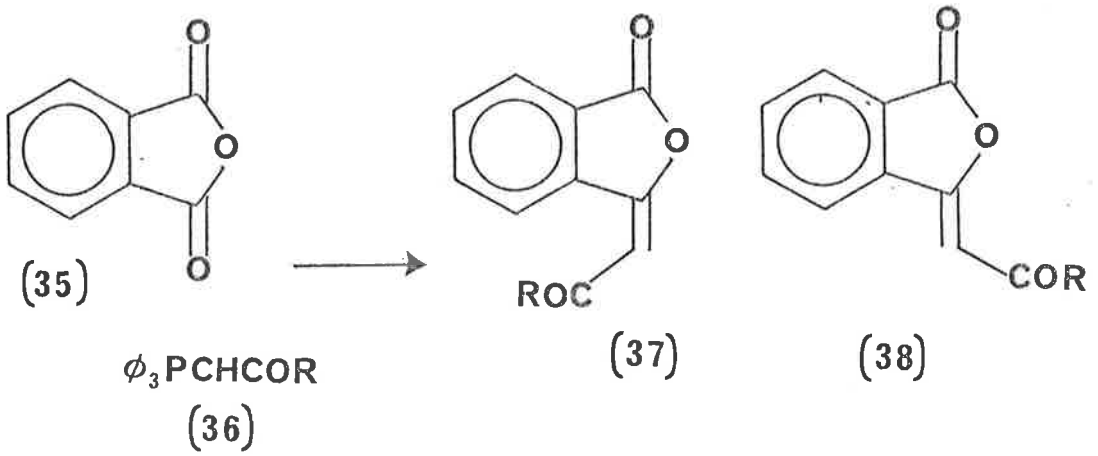


(32) (33) (34)

The stereochemistry of the two isomers was easily assigned from their spectra; in particular H7 in the (E) isomer is considerably deshielded, whereas in the (Z) isomer the four aromatic protons absorb at a similar chemical shift[26]. In this case the olefinic proton H_a in the (Z) isomer absorbs at lower field than in the (E) isomer. This exception is presumably due to deshielding of this proton by the aromatic ring in the (Z) isomer and the absence of deshielding of this proton by a lactone oxygen in the (E) isomer, which in the case of the phthalic anhydride derived enol-lactones has the effect of shifting the absorbtion of H_a in the (E) isomer to slightly lower field than the (Z) isomer.

The factors affecting the stereochemistry of enol-lactones formed from anhydrides and stabilised phosphoranes are poorly understood and several hypotheses have been put forward to explain the observed results.

Chopard[26] noted that in a series of reactions of phthalic anhydride (35) with stabilised phosphoranes the proportion of (E) enol-lactones (37) decreased as the substituent R of the phosphorane (36) was changed from a good electron donor to a poor electron donor.

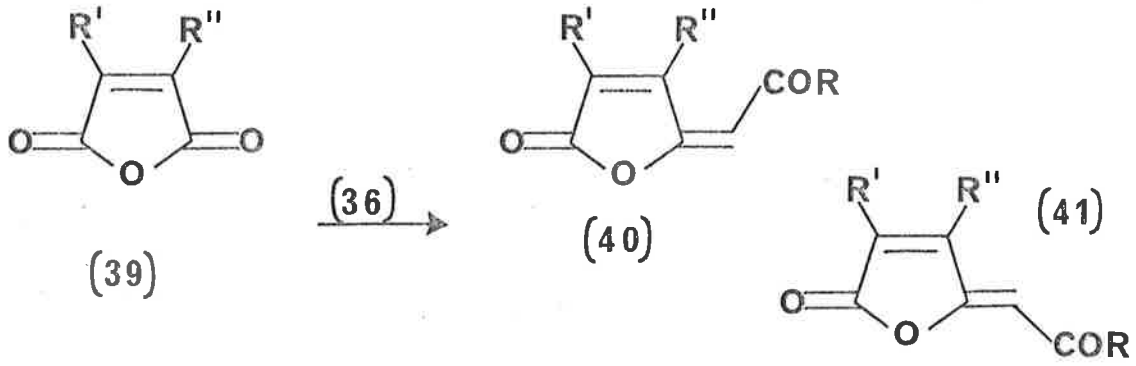


He proposed that a $\pi - \pi^*$ interaction of the RCO group with the aromatic ring in the intermediate betaine accounted for the preference for the (E) isomer (37). This was at a maximum when the substituent R was a good electron donor. Subsequent investigations[14] have shown that the ratios of enol-lactone products were incorrect, although the general trend was the same. Later work has also shown that the reaction of succinic anhydride with the phosphorane (29) gave only the (E) isomer and that substituted maleic anhydrides gave a predominance of the thermodynamic product, the (Z) isomer, upon reaction with the phosphorane (36) ($R=CH_3$)[14], showing that the proposed π interaction was not the only factor involved in determining the product stereochemistry.

An hypothesis put forward by Schlosser[28] to rationalise the results obtained from the reaction of phthalic anhydride with stabilised phosphoranes suggests that when the (E) enol-lactones are formed, the reaction is subject to kinetic control[28]. This occurs when the rate of triphenylphosphine oxide elimination from the intermediate betaine becomes greater than the rate of equilibration of the initially formed betaines. With less nucleophilic phosphoranes e.g. (36) ($R = CH_3$) the rate of decompositon of betaine to product is considered to be reduced, allowing time for the betaines to equilibrate ; consequently the thermodynamic product, the (Z) enol-lactone, is formed. It has subsequently been shown by isomerisation experiments that in the case of enol-lactones formed from the phosphorane (36), ($R = CH_3$) that the (Z) isomer is indeed

thermodynamically more stable[14].

When substituted maleic anhydrides (39) were treated with the phosphorane (36) (R=CH_3) the thermodynamic ratio of products (40) and (41) was obtained, while in the case of the phosphorane (36) (R=OEt) the kinetic product (40) was favoured. As was noted previously, the reaction of the phosphorane (36) (R=OEt) with succinic anhydride and substituted succinic anhydrides again produced only the (E) isomer, which is the kinetic product.



In general it appears that substituted maleic anhydrides give a thermodynamic mixture of products upon treatment with a keto stabilised phosphorane, while an ester stabilised phosphorane gives a predominance of the kinetic product in its reaction with substituted maleic and succinic anhydrides. The reaction of phthalic anhydride with a stabilised phosphorane, on the other hand, appears to give preferentially the kinetic product no matter which phosphorane is employed in the reaction. In cases where the reaction is subject to kinetic control it is possible that the (E) isomer is formed due to dipolar repulsion between the lactone oxygen and the carbonyl group of the

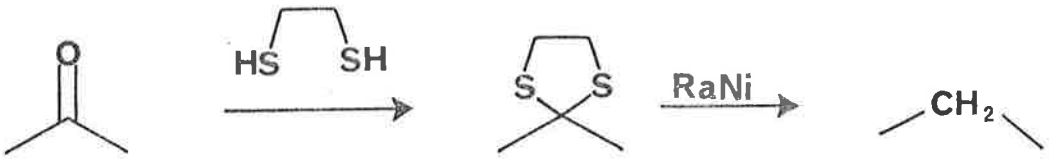
phosphorane. The minimisation of such oxygen-oxygen interaction has been considered to be important in determining the stereochemistry of the product in some reactions of reactive phosphoranes[58]. In substituted maleic anhydrides (39) where R' and R" are large, steric interactions seem to become more important than dipolar repulsion and a predominance of the (Z) isomer is formed. There are however exceptions to this proposal since the reaction of the phosphorane (36) ($R=CH_3$) and dimethylmaleic anhydride (39) ($R', R" = CH_3$) gave mainly the (Z) isomer (41), while the reaction of the same phosphorane with phthalic anhydride (35), which has a similar steric environment around the carbonyl group, gave mainly the (E) isomer.

The present results, obtained from the reaction of thioanhydrides and the phosphorane (29), tend to support the proposal that dipolar repulsion in the intermediate betaine is an important factor governing the stereochemistry of the product. Succinic anhydride (18), for example, gave only the (E) enol-lactone upon treatment with the phosphorane (29), while with the same phosphorane succinic thioanhydride (28) gave a 1:1 mixture of (E) and (Z) isomers. This can be explained by the replacement of the oxygen-oxygen interaction in the case of the succinic anhydride reaction with an oxygen-sulphur interaction in the case of succinic thioanhydride. This oxygen-sulphur interaction would be expected to be small, judging from the effect the ring sulphur has on the chemical shift of the adjacent olefinic proton; a lactone oxygen greatly deshields an adjacent

olefinic proton[14], while a ring sulphur has virtually no effect on this proton [see spectral data for compounds (30) and (31)]. The isomer ratio of the enol-lactones produced from succinic thioanhydride would therefore appear to be controlled only by steric effects. The apparently similar reaction between succinic anhydride and the thioester stabilised phosphorane (5) would only be expected to give the (E) enol-lactone since there is still the possibility of an oxygen-oxygen interaction in the intermediate betaine in this reaction. The reaction of phthalic thioanhydride (32) and the phosphorane (29) also gave results consistent with the proposal that dipolar repulsion in the intermediate betaine is an important factor which can lead to the formation of the (E) enol-lactone product in such a reaction. In this case, the reaction of phthalic anhydride with the phosphorane (29) produced (E) and (Z) isomers in the ratio 9:2 while the reaction with phthalic thioanhydride, where an oxygen-oxygen interaction does not exist, produced (E) and (Z) isomers in the ratio 1:6. The (Z) isomer of these enol-lactones was again shown to be the more stable by the complete isomerisation of the (E) isomer (33) to the (Z) isomer (34) upon standing in chloroform solution.

1.4 Treatment of sulphur-containing enol-lactones with Raney nickel

The reduction of a carbon-sulphur bond in a molecule by treatment of the compound with Raney nickel is a well established procedure [29-31]. An important application of this reaction is, for example, the conversion of a carbonyl group to a methylene group by reduction of the derived thioacetal with Raney nickel[32-4] (Scheme 7).



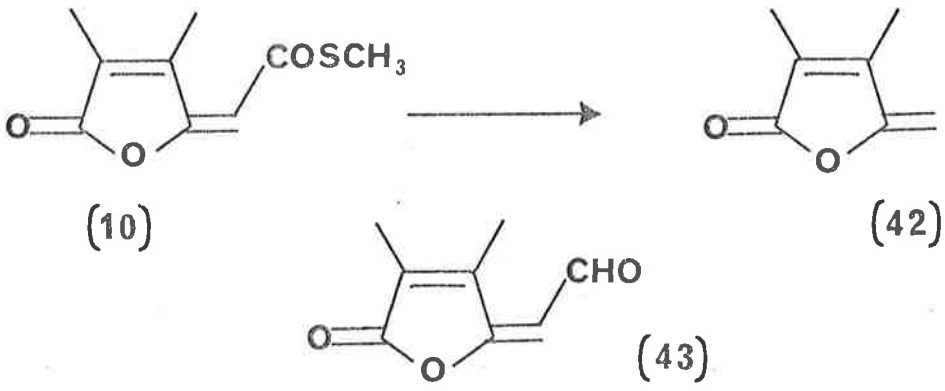
Scheme 7

Scheme 8

This procedure has also been used for the conversion of thioesters to the corresponding aldehydes[35-41] or alcohols[42-5] (Scheme 8); the reduction generally proceeds to the alcohol, unless the Raney nickel is first partially deactivated, for example, by heating it under reflux in acetone or formalin. From these observations it seemed reasonable to expect that thioester enol-lactones could be reduced to the corresponding aldehydes with the proper choice of conditions, although there was a possibility that there might be difficulties due to partial

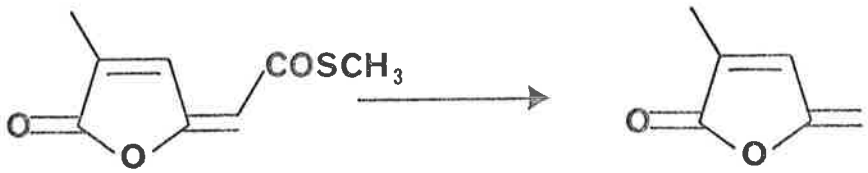
reduction of other double bonds in the molecule .

The enol-lactone (10) was used for the initial investigation of reduction conditions. When a solution of this enol-lactone in ethanol was heated under reflux with a tenfold excess of W-2 Raney nickel[46] for two hours all starting material was consumed, however no UV absorbing products could be detected.



Since these reaction conditions were obviously too vigorous, the use of a partially deactivated Raney nickel was next investigated. Treatment of the enol-lactone (10) in acetone with a fivefold excess of Raney nickel, which had previously been heated in boiling acetone for one hour, produced a mixture of starting material and one product, which was identified as (42)[47]; no trace of the expected aldehyde(43) could be detected. Further investigation showed the optimum reaction conditions to be the treatment of the enol-lactone in reluxing actone with twenty times its weight of Raney nickel which had previously been heated in boiling acetone for thirty minutes. Under these conditions the enol-lactone(42) was obtained in good yield as the only product.

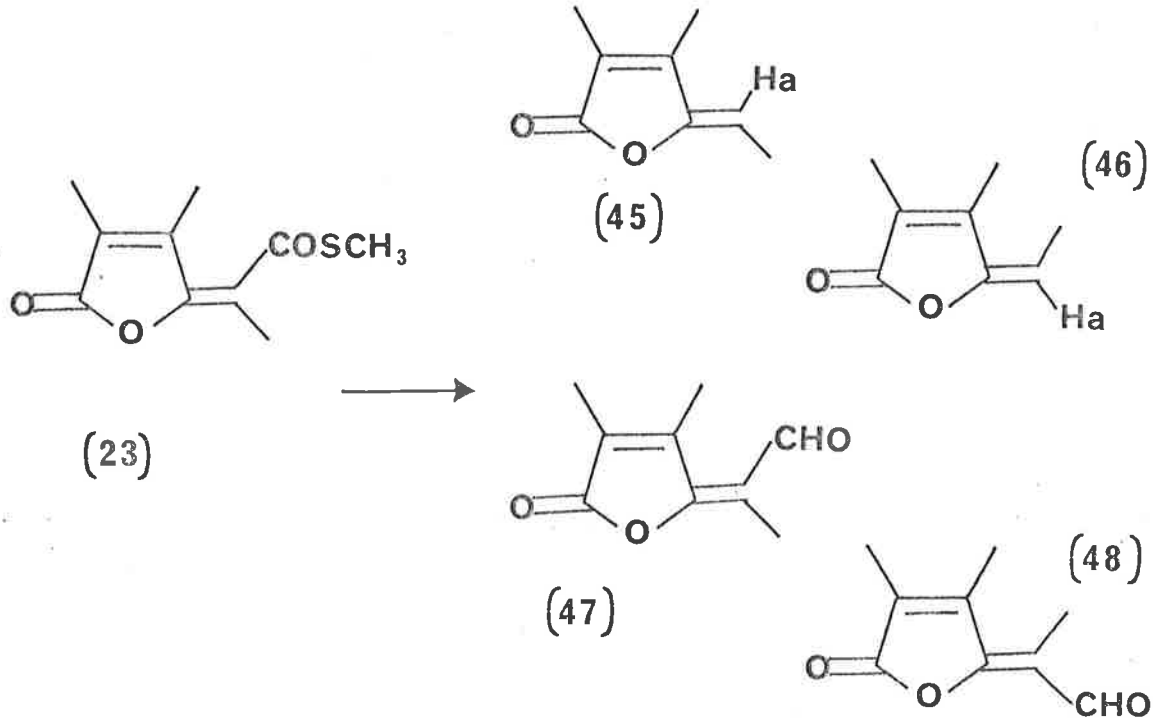
Treatment of the enol-lactone (13) with Raney nickel under the above conditions again gave a good yield of the alkylidenefuran - 2(5H) - one (44)[48], with no detectable formation of aldehyde.



(13) (44)

Due to the surprising nature of the products from these two reactions, the reactions were repeated using a freshly prepared batch of Raney nickel. Identical results were obtained with almost identical yields.

At this stage it seemed that this reaction could be general for this type of enol-lactone, and this was borne out by further experiments. When the enol-lactone (23) was treated with Raney nickel four products were obtained.

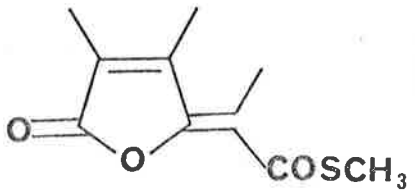


(23) (45) (46) (47) (48)

The major product was (45)[12] where loss of the thioester group had occurred largely with retention of stereochemistry about the double bond. A small amount of (46) where isomerisation had taken place about the double bond, was also formed. The two isomers were distinguished, as in previous sections, by the chemical shift of the protons H_a. Thus in the (Z) isomer (45) H_a absorbs at δ 5.23 while in the (E) isomer (46) it absorbs at δ 5.75, due to deshielding by the lactone oxygen. On the assumption that this reaction proceeds mainly with retention of configuration, which later examples appear to bear out, this result confirms the stereochemistry of the enol-lactone (23), which was originally in some doubt. The two remaining minor products formed in this reaction were the (E) and (Z) aldehydes (47) and (48), which were formed in approximately equal amounts; the stereochemistry of these aldehydes could not, however, be unambiguously assigned. The extent of deactivation and quantity of Raney nickel used were again varied for this reaction, but the amount of aldehyde formed could not be increased.

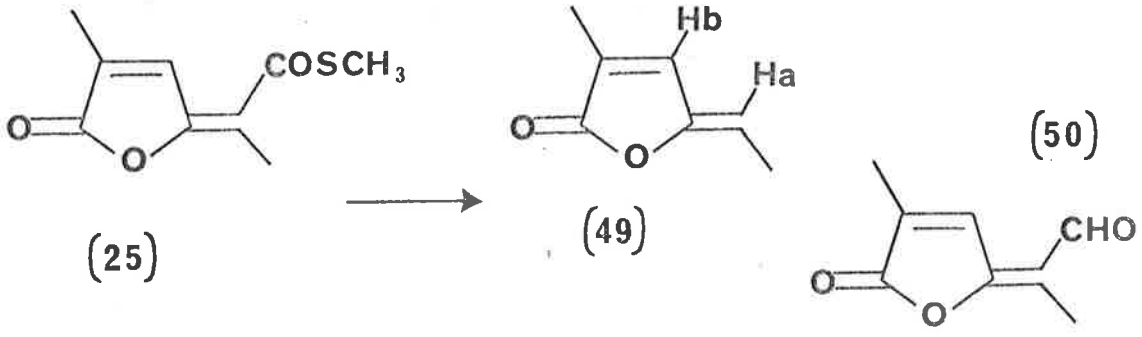
This reaction offers a useful route to 5-alkylidenefuran - 2(5H)-ones with advantages over other methods, such as the treatment of an anhydride with a Grignard reagent followed by dehydration of the resulting alcohol[12], in that either isomer can be produced stereoselectively, while with other methods only the thermodynamic product is generally formed[27].

In order to confirm the apparent stereoselectivity of the desulphurisation reaction, the reaction of the isomeric enol-lactone (24) with Raney nickel was next investigated. Under the usual reaction conditions four products were again produced. The major product formed was the (E) 5-alkylidenefuran- 2(5H)-one (46) resulting from loss of the thioester group again with retention of stereochemistry, as in the previous example. Small amounts of the (Z) isomer (45) and the (E) and (Z) aldehydes, (47) and (48) were also formed.



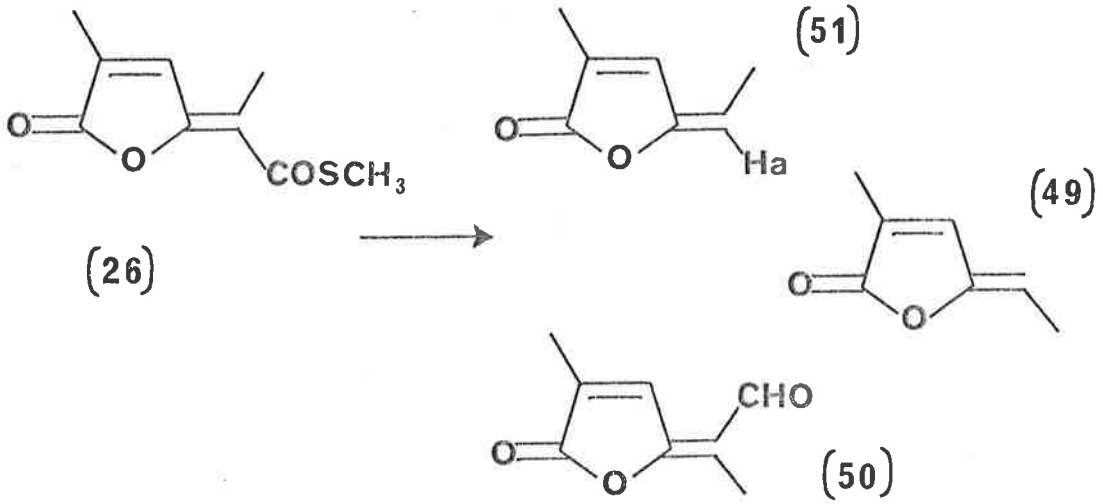
(24)

Two further examples which illustrated the loss of the thioester group upon treatment of the compound with Raney nickel, and the stereoselective nature of the reaction, were the enol-lactones (25) and (26). When the enol-lactone (25) was heated in boiling acetone with partially deactivated Raney nickel, an excellent yield of the alkylidenefuran -2(5H)-one (49)[11] was obtained. The stereochemistry of this product was assigned as (Z) on the basis of the chemical shift of the proton H_a (δ 5.2) which was virtually identical to the corresponding proton in (Z) -3,4 - dimethyl - 5 - ethylidenefuran - 2(5H) - one (45) (δ 5.23). A very small amount of the aldehyde (50) was also formed. The stereochemistry of this compound was readily determined to be (E) since proton H_b had a very similar chemical shift (δ 7.77) to the corresponding proton in the starting enol-lactone (δ 7.9).



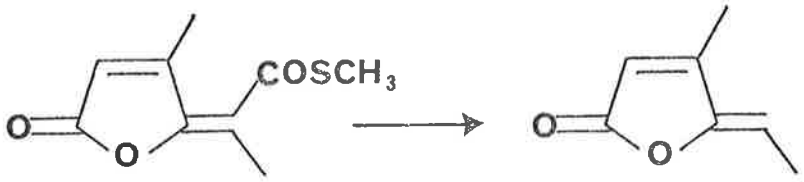
(25) (49) (50)

The isomeric enol-lactone (26), upon treatment with Raney nickel, gave three products. The major product was again an alkylidenefuran -2(5H)-one (51), produced with retention of the stereochemistry about the double bond; the (E) stereochemistry was apparent from the chemical shift of proton H_a (δ 5.67), compared with δ 5.2 for the same proton in the product (49) from the previous reaction.



(26) (51) (49) (50)

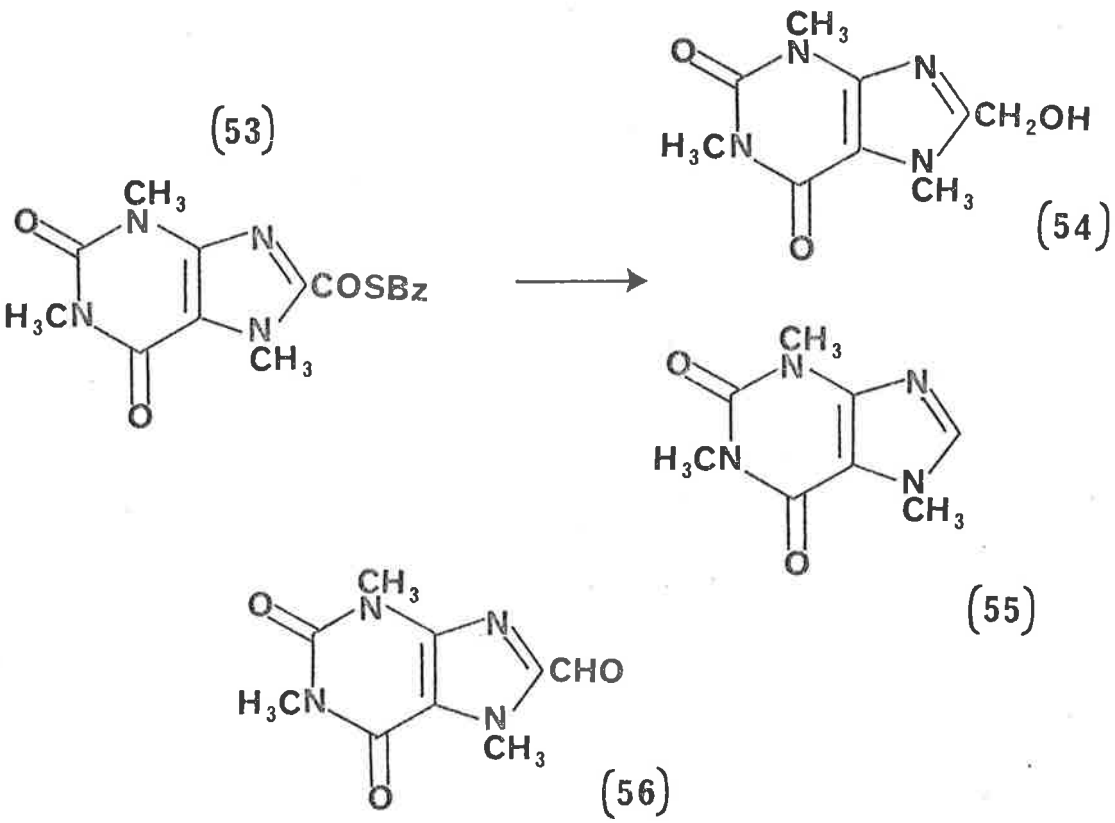
The (Z) alkylidenefuran -2(5H)-one (49) and the (E) aldehyde (50) were formed as minor products. No trace of the (Z) aldehyde could be detected in the reaction mixture; it is possible that under the reaction conditions the aldehyde isomerises to the thermodynamically more stable isomer.



(27) (52)

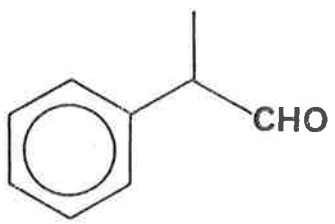
The Raney nickel desulphurisation reaction was now used to assign the stereochemistry of the enol-lactone (27). Upon treatment with Raney nickel, the enol-lactone (27) gave (Z) - 4 - methyl - 5 - ethylidenefuran - 2(5H) - one (52)[11] as the only identifiable product. The stereochemistry of this known product was the basis for the assignment of (E) stereochemistry for the starting enol-lactone, which could not be assigned by the NMR data available.

Only one example where complete loss a thioester group had occurred upon treatment of a compound with Raney nickel could be found in the literature[49].

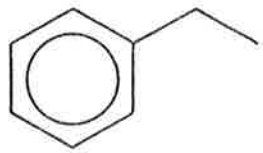


(53) (54) (55) (56)

In this example treatment of the caffeine derivative (53) with Raney nickel in ethanol or dioxane produced a mixture of the alcohol (54) and caffeine (55). In a further experiment the aldehyde (56) was found to give a moderate yield of the alcohol (54) and an unstated amount of caffeine (55) when it was treated with Raney nickel. From this the authors concluded that the reduction of the thioester occurred in two steps; the ester was first reduced to the aldehyde and then the aldehyde was either reduced to the alcohol or lost carbon monoxide to give the completely decarbonylated product. Later work by Zderic and co-workers[50] seemed to support this hypothesis. They found that when certain aromatic aldehydes or alcohols were treated with Raney nickel, products arising from the formal loss of carbon monoxide were formed; for example, treatment of the aldehyde (57) with Raney nickel produced mainly ethylbenzene (58) along with a small amount of cumene (59).



(57)



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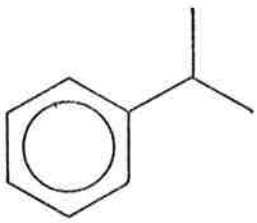
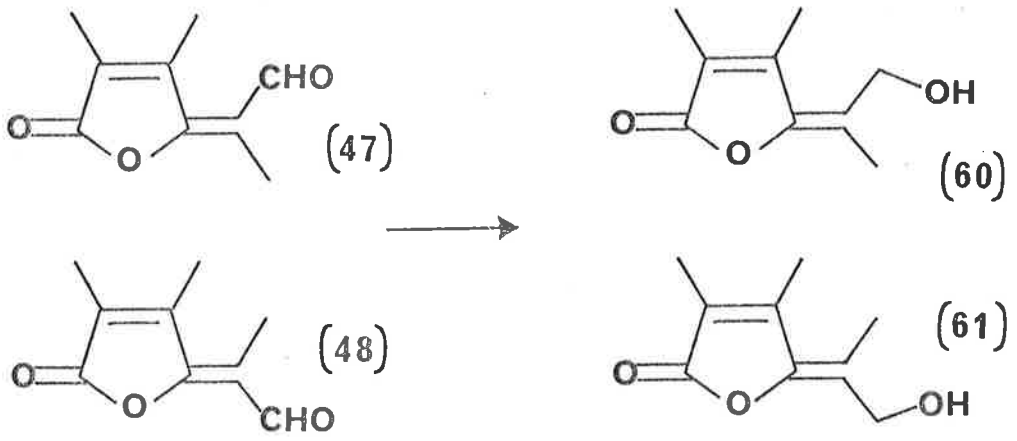


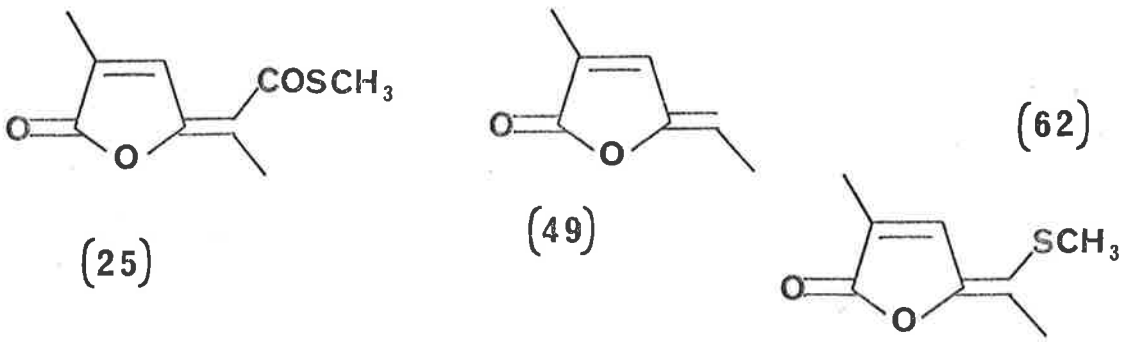
(59)

With this in mind the mixture of (E) and (Z) aldehydes (47) and (48), obtained as a minor product from the treatment of the enol-lactone (23) with Raney nickel, was retreated with Raney nickel under the same reaction conditions as had been used for the original reduction. This reaction gave an excellent yield of the alcohols (60) and (61), however, no alkylidenefuranone could be detected,

suggesting that the aldehyde is not an intermediate in the reduction of these thioesters.

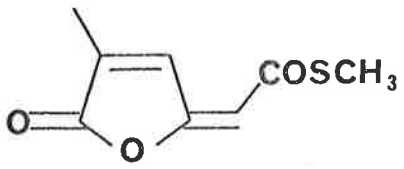


A clue to the mechanism of the reduction came from the treatment of the enol-lactone (25) with a fifteenfold excess of Raney nickel, rather than the twentyfold excess which was used previously. Under these conditions some starting material was recovered along with two products.



One product was the alkylidenefuran - 2(5H)-one (49) which had been isolated previously, while the other was the thioenol ether (62), formed by loss of carbon monoxide from the thioester. Further treatment of this thioenol ether with Raney nickel afforded a good yield of the alkylidenefuran -2(5H)-one (49), suggesting that this was the route by which the decarboxylated products were formed.

Another example where an intermediate could be isolated was found when the enol-lactone (13) was treated with a tenfold excess of Raney nickel (rather than a twentyfold excess).



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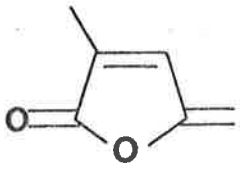
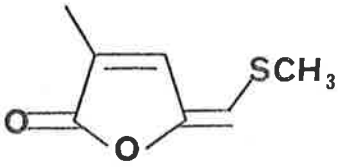


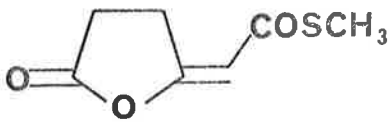
(44)

(63)



Here again starting material was isolated along with two products, the decarboxylated material (44) isolated previously and the thioenol ether (53), resulting from extrusion of carbon monoxide. As expected, treatment of this thioenol ether with Raney nickel gave a good yield of the alkylidenefuran -2(5H)-one (44). The formation of a thioether, with the loss of carbon monoxide, from an aromatic thioester upon treatment with degassed Raney nickel has been previously observed[51,52].

It seemed likely that the extensive unsaturation of the thioester group in the compounds investigated was responsible for the unexpected loss of this group upon treatment with Raney nickel, since examples in the literature where aldehydes had been isolated from this type of reduction were generally saturated thioesters. The reduction of a less conjugated thioester enol-lactone might therefore show whether such extended conjugation is necessary for the loss of the thioester group to occur. A suitable enol-lactone was compound (19).



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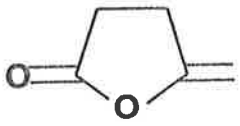
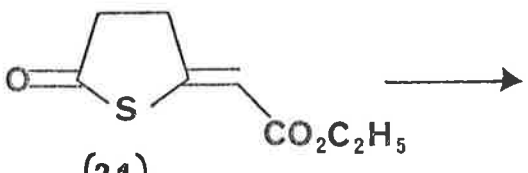


(64)

When (19) was treated with Raney nickel the only product was the expected 5 - methylidene - tetrahydrofuran - 2 - one (64)[53]. It is likely that the low yield is due to the instability of this compound.

An example in which the thioester is fully saturated is the thiolactone (31). This compound proved to be more stable to reduction than the examples previously investigated. Thus even when this thiolactone was treated with as much as a thirtyfold excess of Raney nickel for 48 hours some starting material could still be recovered. The only product detected was the formyl ester (65) which is the product that one would normally expect from a Raney nickel reduction. This product was inseparable from starting material and was therefore isolated as the diester (66)[54], formed by treating the mixture of compounds with ethoxycarbonylmethylene - triphenylphosphorane (29).



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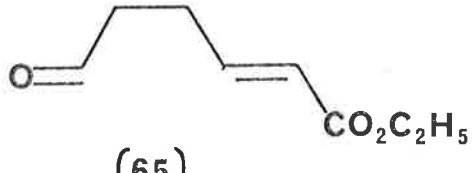

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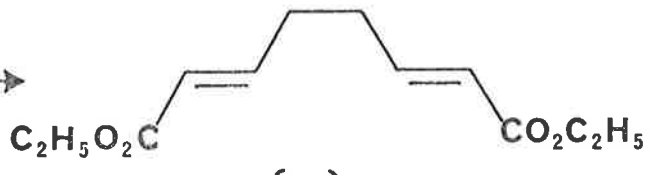
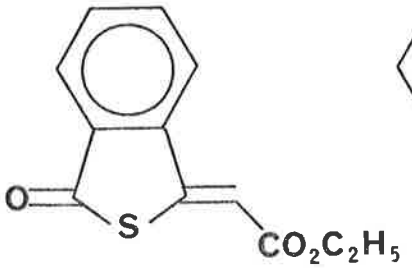
(29)



(66)

The reduction of another thiolactone (34) in which the thioester group was now conjugated gave completely different results to those in the previous example.



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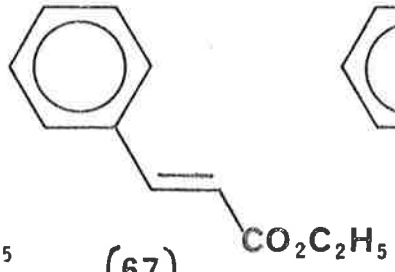
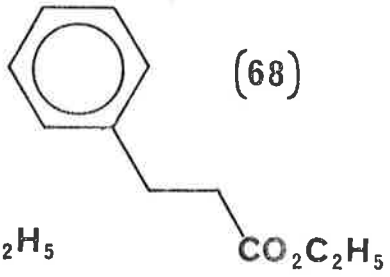


(67)



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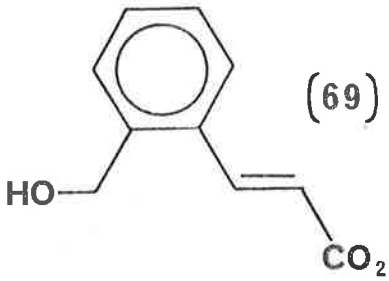

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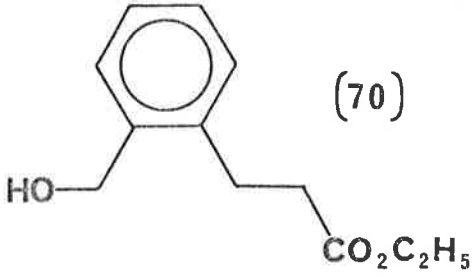
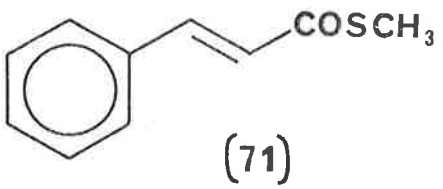


(70)

The compound (34) again proved moderately difficult to reduce; starting material was isolated from the reaction mixture along with four products. The two major products were ethyl cinnamate (67) and ethyl 3-phenylpropanoate (68), formed by complete loss of the thiolactone group as had been noted for most of the previous examples. The two minor products (69) and (70) are those normally expected from a Raney nickel reduction.

As a final example S-methyl thiocinnamate (71)[55] was treated with Raney nickel. The reduction was again very slow and starting material could be isolated from the reaction mixture together with cinnamaldehyde (72) which was the only product; no styrene (73) could be detected.



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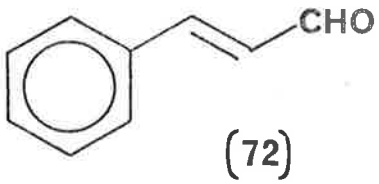

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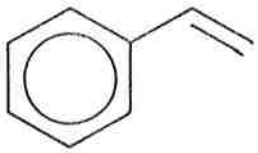
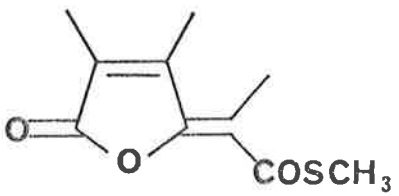


(73)

It therefore appears that although the thioester must be unsaturated for cleavage rather than reduction to occur, other factors must also be involved since S-methyl thiocinnamate, for example, gave only a reduction product.

Overall, the treatment of thioester enol-lactones such as (24) with Raney nickel offers a convenient stereoselective route to 5-alkylidenefuran -2(5H)-ones such as (46). The (E) and (Z) isomers of the required enol-lactones can be easily prepared from the corresponding anhydrides by treatment with a thioester stabilised phosphorane, e.g. (21).



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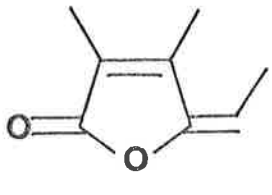

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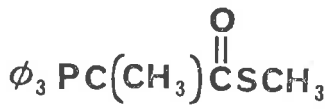
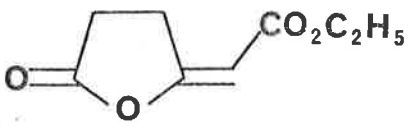


(21)

1.5 Reactions of enol-lactones with stabilised phosphoranes

As an extension of the investigation of enol-lactones as synthetic intermediates, the reaction of stabilised phosphoranes with a variety of enol-lactones was investigated.

Treatment of ethyl (E) - 5 - oxotetrahydrofuran - 2 - ylideneacetate[14] (20) with ethoxycarbonylmethylene triphenylphosphorane (29) in carbon tetrachloride gave a moderate yield of products (76) and (77) in the ratio 5:2.



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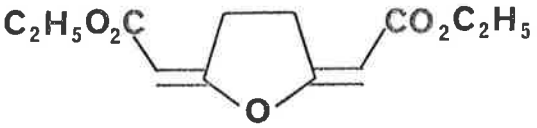
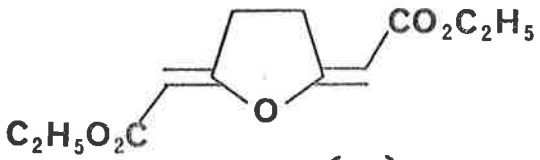


(76)

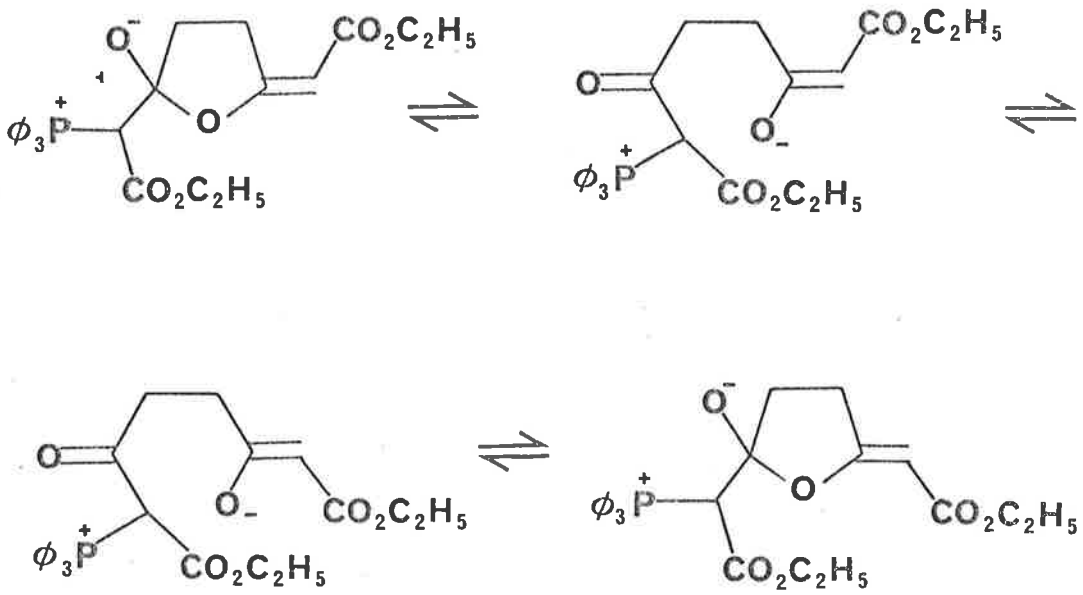


(77)

(29)

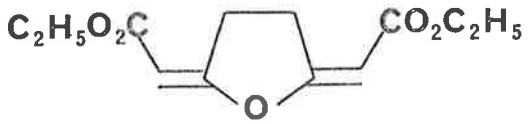
The (E,E) isomer was the major product, as was generally the case in the reaction of anhydrides with ester stabilised phophoranes to produce enol-lactones[14]. The assignment of the stereochemistry of these two compounds was based on spectral data. In particular, compound (76) has only one olefinic hydrogen resonance in its ^{1}H NMR spectrum because of the symmetry in the molecule, while (77) has two resonances (δ 5.2 and δ 5.8). By analogy with the chemical shifts of the olefinic hydrogens in enol-lactones[14], the (E) configuration was assigned to the enol ether carrying

the more deshielded proton. It was also probable that the configuration in the symmetrical product (76) would be the same as that in the starting enol-lactone (20). However, the stereochemistry of (20) could have been changed due to ring-opening after addition of the phosphorane to the lactone carbonyl, (Scheme 9).



Scheme 9

It was found that the bis-enol ether (76) could be isomerised to the corresponding furan derivative (78) by heating in chloroform solution containing a trace of trifluoroacetic acid. The ester was hydrolysed and isolated as the diacid (79). Substituted furans should be generally accessible from substituted succinic anhydrides by this route.



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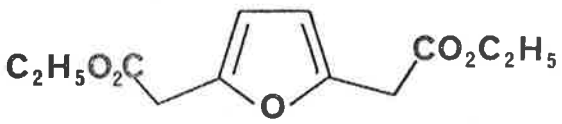
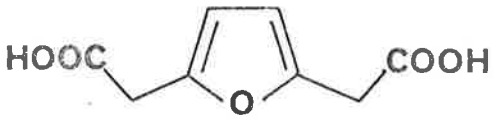
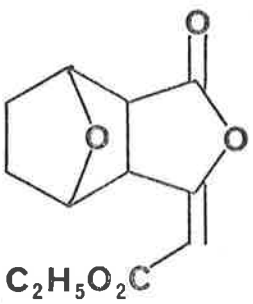


(78)

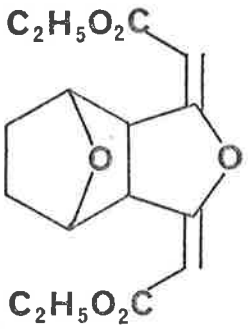


(79)

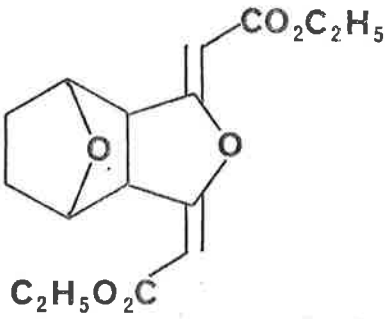
An example similar to the enol-lactone (20) previously investigated was ethyl (E, 3aβ, 4α, 7α, 7aβ) - 3 - oxo - perhydro -4,7- epoxyisobenzofuran -1- ylideneacetate (80). When this compound was treated with the phosphorane (29) a good yield of the two bis-enol ethers (81) and (82) in the ratio 20:1 was obtained. The stereochemistry was assigned as (E,E) for the major product (80) and (Z,E) for the minor product (82) on the same basis as the previous example. Thus the (E,E) product has an olefinic resonance at δ 5.6 while the (Z,E) product has olefinic absorbtions at δ 5.2 and δ 5.7. The same assumption about the stereochemistry of the symmetrical product again applies.



(80)



(81)



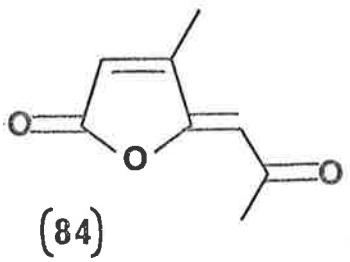
(82)

The less reactive phosphorane (83) did not react with the enol-lactones (20) and (80) under the same conditions used with the phosphorane (29); even when the reaction mixtures were maintained at 90° for several hours, no products could be isolated.

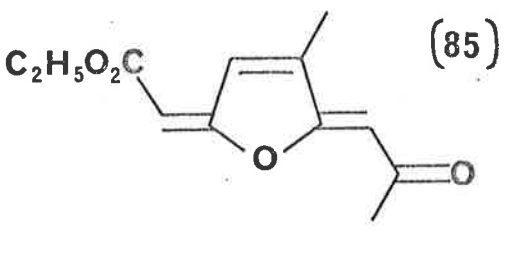
$Ph_3PCHCOCH_3$ (83)

The next two examples examined contained both a lactone and a ketone carbonyl group and the possibility therefore existed for reaction to occur at either or both of these centres.

Treatment of the keto-lactone (84)[14] with the phosphorane (29) gave three products, two of these, (85) and (86), arising from reaction at the lactone carbonyl and the third (87) from reaction at the keto carbonyl. The major product was (85), arising from reaction at the lactone carbonyl. The stereochemistry of this product was assigned on the basis of the chemical shift of H4 (δ 7.5) which indicated (E) stereochemistry[14].



(84)



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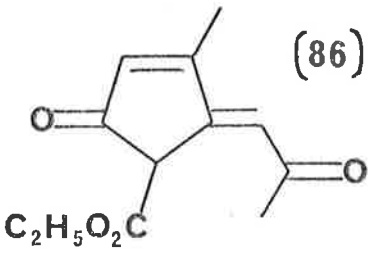
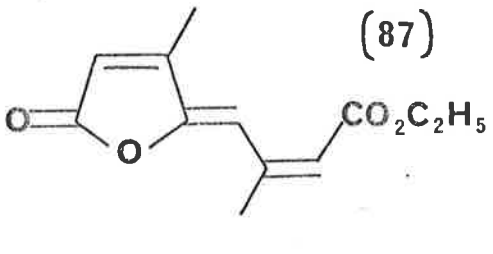
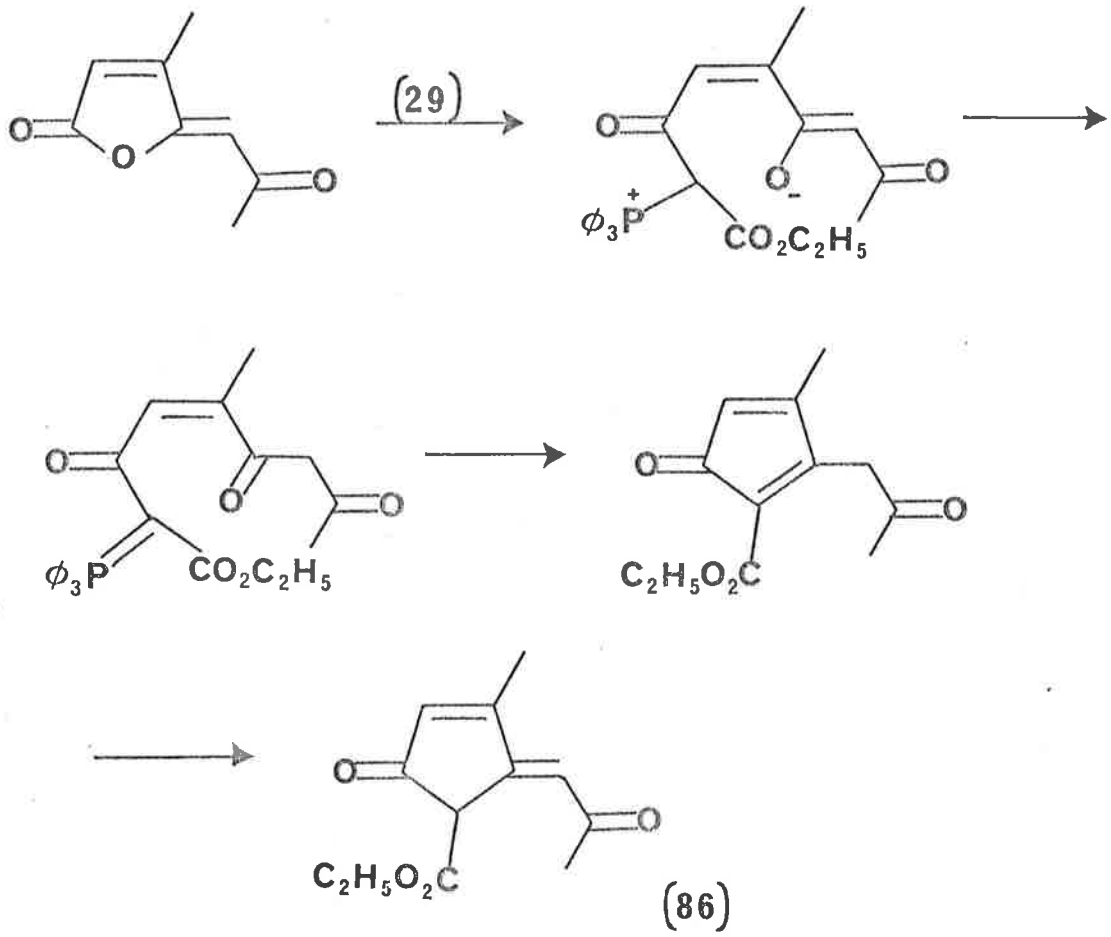


(86)



(87)

The fact that reaction had occurred at the lactone carbonyl as confirmed by the absence of a lactone carbonyl stretch in the infrared and the presence of one ester and one ketone carbon in the ^{13}C NMR spectrum. The other product (86) arising from reaction at the lactone carbonyl was presumably formed by addition of the phosphorane to the lactone carbonyl followed by ring opening and an intramolecular Wittig reaction (Scheme 10).

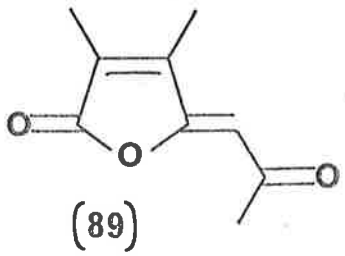


Scheme 10

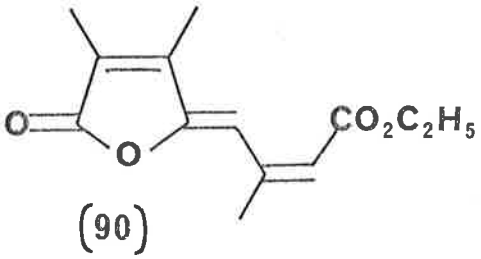
This same process has been observed in the reaction of reactive phosphoranes with enol-lactones[60] and more recently in the reactions of anhydrides with stabilised phosphoranes[17,61] The structure of (86) was confirmed by the presence of two ketone and one ester carbon in the ^{13}C NMR spectrum and one D_2O exchangable proton (δ 4.3),

(H1), in the proton NMR spectrum. The third product (87) formed in this reaction was shown to be derived from reaction at the ketone carbonyl by the presence of a lactone carbonyl stretch in the infrared and the presence of two ester or lactone carbons in the ^{13}C NMR spectrum of this compound. The stereochemistry of the product was assigned as (E) on the basis of the chemical shift of H4', (δ7.5) which indicates deshielding by the adjacent carbonyl group. The assignment of the olefinic protons in the ^{1}H NMR spectra of these compounds was checked by repeating the reaction with the deuterated phosphorane (88).

Ph_3PCDCO_2Et (88)



(89)



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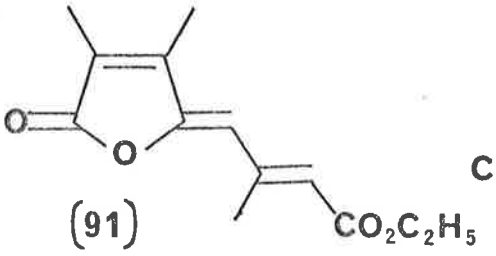
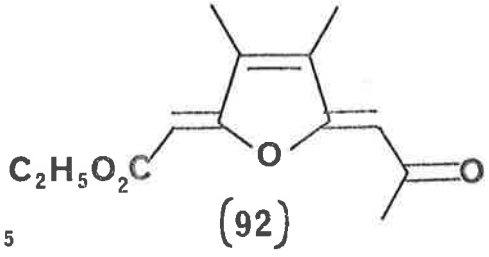


(91)

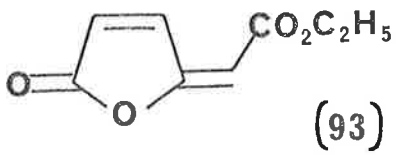


(92)

The reaction of the keto-lactone (89)[14] with phosphorane (29) again gave three products. Reaction had occurred mainly at the ketone carbonyl; the small amount of product (92), derived from reaction at the lactone carbonyl, compared to (84), is probably due to the steric effect of the C4' methyl group.

The structures of the products (90) and (91) were confirmed by the presence of a lactone carbonyl absorbtion in their infrared spectra and two ester or lactone carbons in their ^{13}C NMR spectra. The stereochemistry of these products is indicated by the chemical shift of H4: this is δ 7.43 in the major product (90), due to deshielding by the ester carbonyl group and δ 5.36 in (91). The stereochemistry of the new enolic double bond in the minor product (92) was assigned by comparison of the ^{1}H NMR chemical shift of H2 in this compound (δ 5.3) with that of the corresponding proton in product (85),(δ 5.7); this difference suggests the opposite stereochemistry about the enolic double bond in these two compounds and since the (E) stereochemistry of (85) is unambiguous, the stereochemistry of (92) must be (Z). The assignment of the olefinic protons in the ^{1}H NMR spectra of these compounds was again checked by repeating the reaction with the deuterated phosphorane (88).

Treatment of the enol-lactone (93)[14] with phosphorane (29) yielded a dark tar from which no products could be isolated.

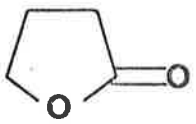


(93)

This problem had also been encountered in the treatment of maleic anhydride with this phosphorane[16]. It was proposed that the tar formation could be due to Michael-type addition

of the phosphorane to the double bond. In that case the problem was overcome by protecting the double bond as a Diels-Alder adduct with furan, however this was not investigated in the present example.

The fact that enol-lactones react with stabilised phosphoranes seems to be due to the delocalisation of the electron pairs on the lactone oxygen over an extended π system. This was demonstrated by the reaction of various simple lactones and enol-lactones with a stabilised phosphorane. As would be expected butyrolactone (94) proved to be completely inert towards to phophorane (29).



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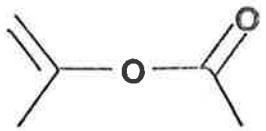

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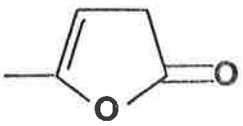
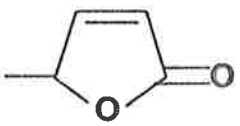
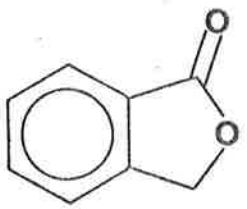


(95)



(97)

The simple enol-lactone α-angelica lactone (5-methylfuran - 2(3H) - one) (95) and isopropenylacetate (96) also proved unreactive; on prolonged heating with phosphorane, α-angelica lactone slowly isomerised to the conjugated isomer (97). As a further example, phthalide (98) also proved to be completely unreactive towards the phosphorane (29), however, Elix[62] has reported a very low yield of product from reaction with cyanomethylene-triphenylphosphorane (99) after 100 hours in boiling xylene.



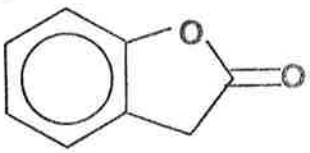
(98)

ϕ_3PCHCN

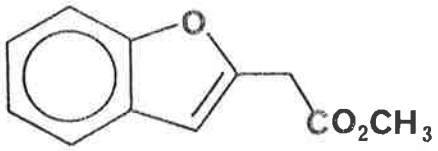
(99)

$\phi_3PCHCO_2CH_3$

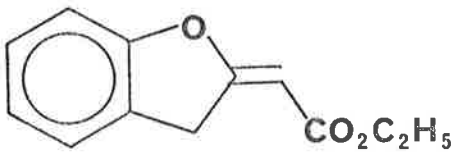
(102)



(100)



(101)



(103)

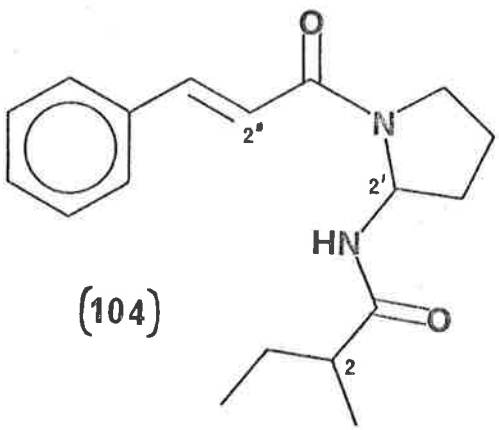
On the other hand, the reactivity of benzofuran-2(3H)-one (100), in which the lone electron pairs on oxygen can be delocalised away from the carbonyl group, has already been demonstrated by the synthesis of methyl 2'-benzofuryl - acetate (101) from reaction with methylcarbonylmethylene triphenylphosphorane (102)[62]. In the present work the reaction was followed by NMR spectroscopy, but the initial Wittig product (103) could not be observed.

CHAPTER 2

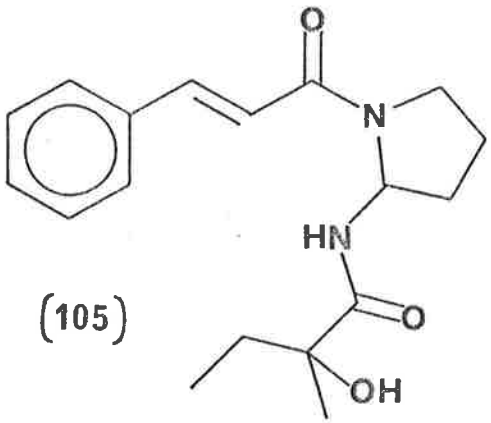
The Stereochemistry of Odorine

INTRODUCTION

Investigation of the leaf extracts of the plant Aglaia odorata Lour. led to the isolation of two new nitrogenous compounds, named odorine and odorinol[69]. Acid hydrolysis of both these compounds yielded cinnamic acid; in addition odorine also afforded 2 - methylbutanoic acid and odorinol afforded 2 - hydroxy - 2 - methylbutanoic acid upon hydrolysis. This information, along with spectroscopic evidence, led to the proposal of structure (104) for odorine and structure (105) for odorinol[69].



(104)



(105)

These same two compounds have more recently been isolated from the leaf extracts of Aglaia roxburghiana [70].

Odorine and odorinol both contain two chiral centres. The stereochemistry at C2 can be readily determined from the optical rotations of the 2 - methylbutanoic and 2 - hydroxy - 2 - methylbutanoic acids obtained on hydrolysis of these compounds, however, the stereochemistry at C2' is relatively inaccessible since hydrolysis would epimerise this centre. The configuration at C2' can therefore be determined only by

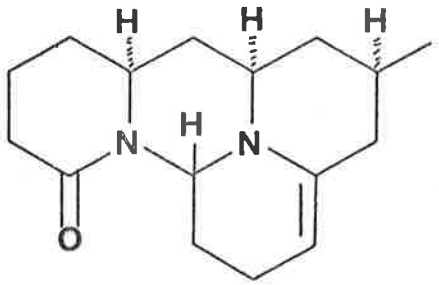
a stereospecific synthesis of these compounds. Synthesis would also serve as proof of the proposed structures.

An N-C-N function would normally be acid labile due to the formation of a resonance stabilised carbonium ion upon heterolysis of the carbon-nitrogen bond (Scheme 11).

Scheme 11

The stability of this function in odorine and odorinol can be explained by the delocalisation of the electrons on nitrogen into the carbonyl system, making these electrons less available for the stabilisation of a carbonium ion centre.

Ayer[71] has shown that catalytic hydrogenation in ethyl acetate of the alkaloid anhydrolycocernuine (106) afforded only a small amount of allocernuine (107); the major product was epiallocernuine (109). The allocernuine had undergone an epimerisation process, presumably via a zwitterionic intermediate of the type (108), to the more stable epiallocernuine (109), (Scheme 12).



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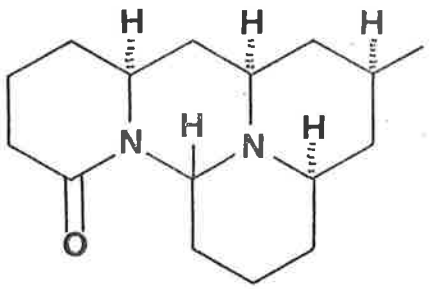

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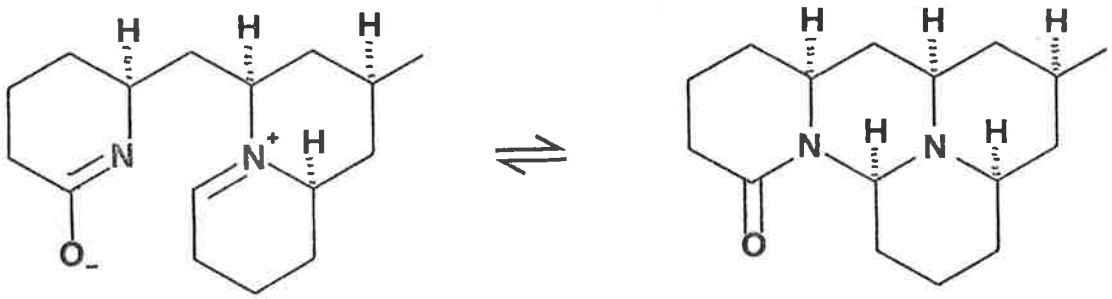
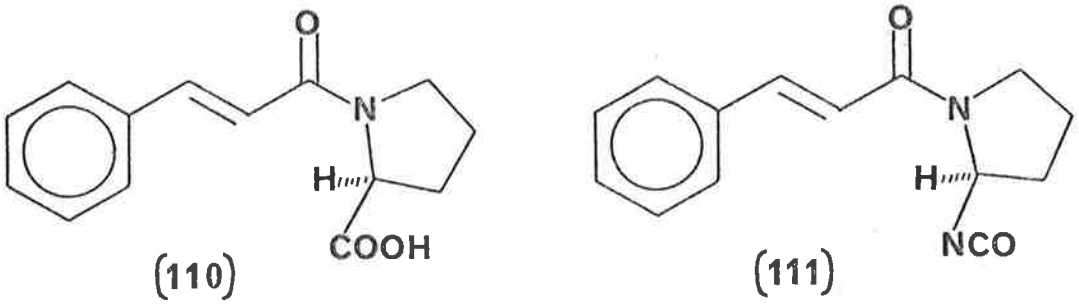


(108) (109)

Scheme 12

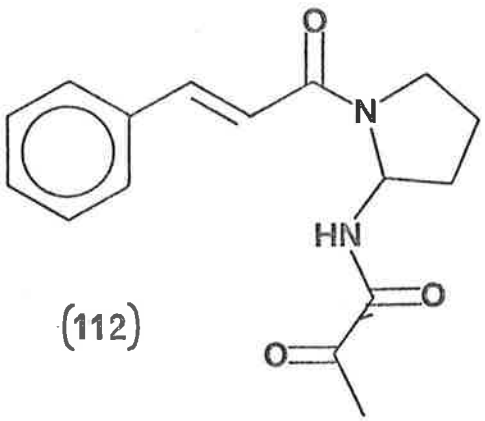
In light of this information, it was considered necessary in the synthesis of (104) or (105) to proceed via precursors in which both nitrogen atoms of the 2 - aminopyrrolidine moiety were conjugated, otherwise the synthesis could be complicated by racemisation at C2'. It was, in fact observed[70] that upon standing in chloroform solution odorine partially isomerised to another compound, epiodorine, presumably epimeric at C2'.

The isocyanate (111) was chosen as a key intermediate from which both odorine and odorinol could be prepared. This isocyanate could be prepared stereospecifically from the optically active acid (110) via a Curtius rearrangement, which is known to proceed with retention of configuration[72,73].



(110) (111)

The final transformation of the isocyanate (111) to odorine (104) could be affected by the addition of a Grignard reagent, in this case 2 - butylmagnesium bromide, to the isocyanate group[74,75]. This reaction would be expected to yield two diastereoisomers of odorine. Similarly, treatment of the isocyanate with an acetyl anion equivalent[76-78] should yield the α - keto amide (112). Treatment of this α - keto amide with ethylmagnesium bromide would be expected to produce odorinol, again as a mixture of two diastereoisomers.



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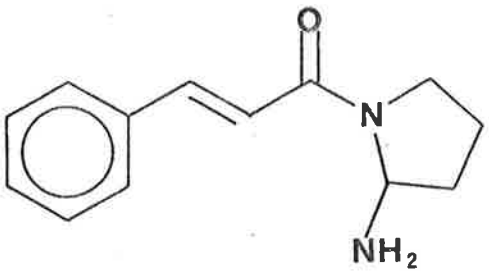
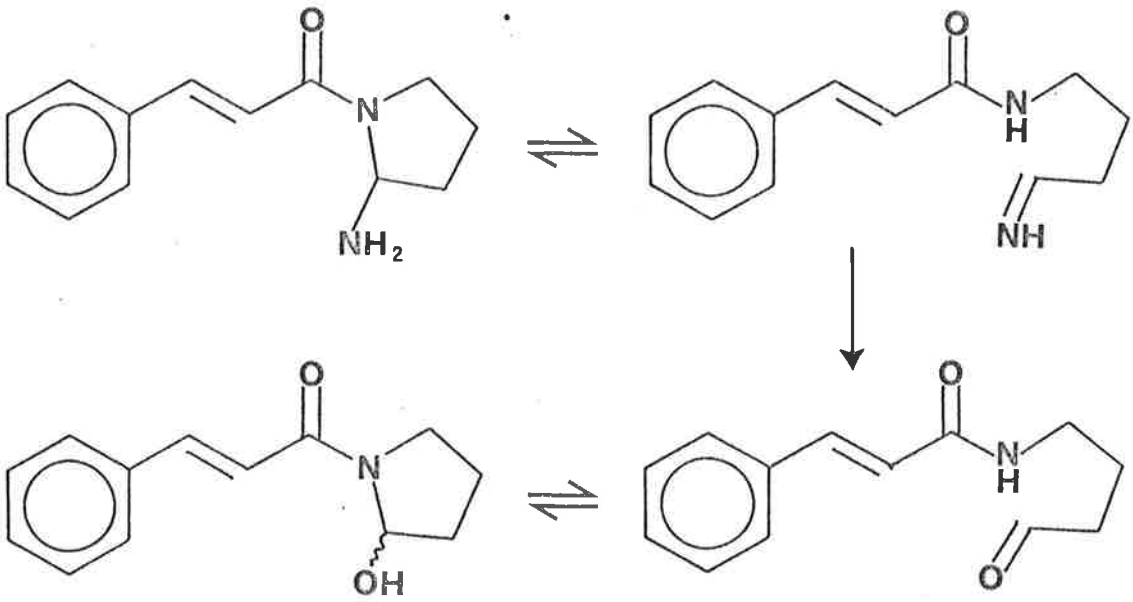


(113)

An alternative synthesis of odorine and odorinol could involve hydrolysis of the isocyanate function of (111) to the amine (113), followed by acylation. This, however, would be better avoided since previous workers have shown that the alkaline hydrolysis of an isocyanate group attached to an asymmetric carbon atom leads to racemisation[79]. This procedure could be further complicated by the reaction of the amine, formed from the isocyanate, with another molecule of isocyanate to form the corresponding urea[80]. Acidic hydrolysis of an isocyanate generally proceeds with

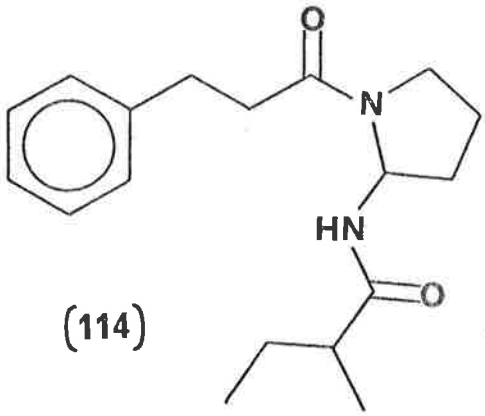
retention of configuration[72]; urea formation is also reduced under these conditions since the amine is protonated, making it less nucleophilic towards another isocyanate molecule. The amine (113) is, however, liable to ring open under acidic conditions since the amine nitrogen is no longer conjugated with a carbonyl group (Scheme 13). Such ring opening has been observed in a penicillin derivative which has the same amide-isocyanate functional group relationship as (111)[81].



Scheme 13

Initial investigations directed towards the synthesis of odorine had centred around the addition of 2 - butylmagnesium bromide to the isocyanate (111)[82]. The reaction proved to be unsuccessful and it was thought that the lack of success might be due to side reactions involving the 2" - 3" double bond.

After considering the above information, it was decided in this present study to attempt the synthesis of dihydroodorine (114) by the addition of 2 - butylmagnesium bromide to the isocyanate (115).



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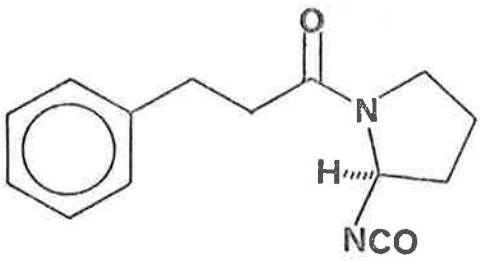


(115)

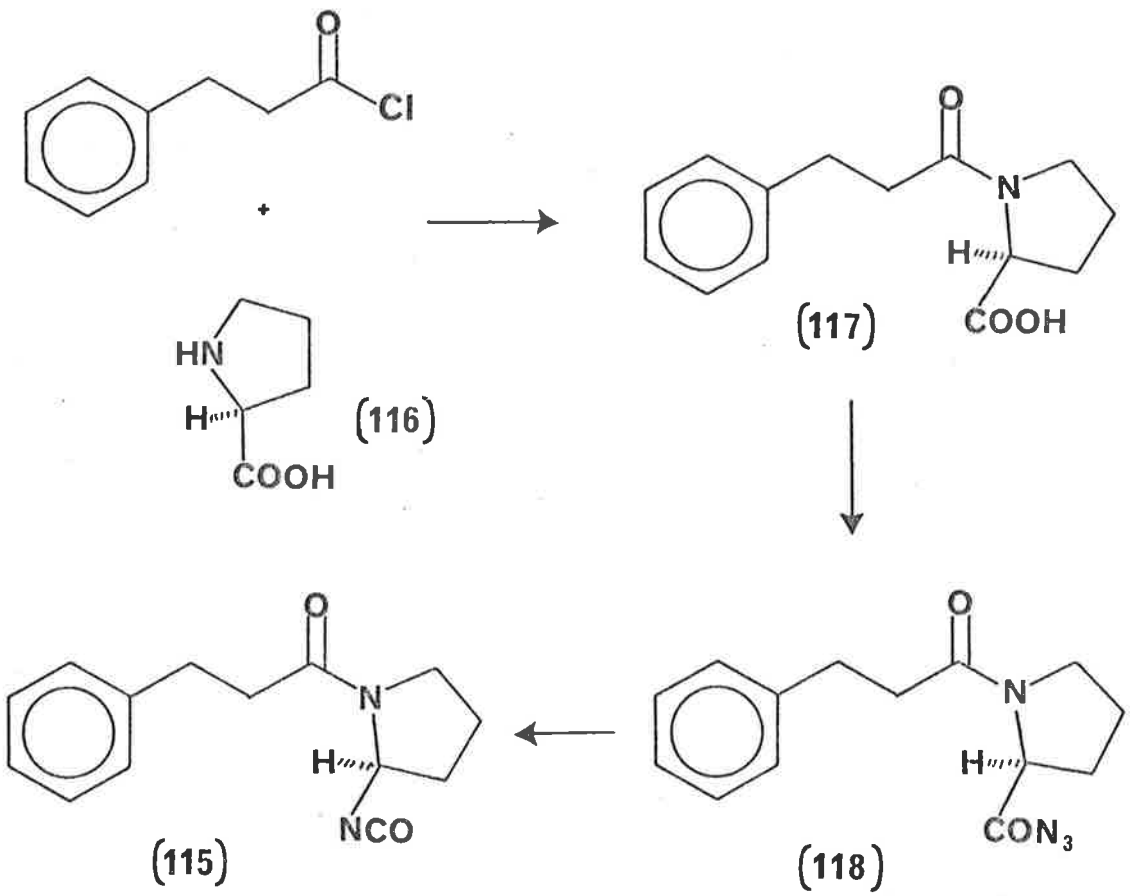
This reaction did in fact give dihydroodorine (114) as a component in a mixture of two diastereoisomers. These isomers proved to be extremely difficult to separate, however a pure sample of dihydroodorine was eventually obtained. Later investigation of the reaction of 2 - butylmagnesium bromide with the unsaturated isocyanate (111) resulted in the synthesis of the two diasteroisomers of odorine itself, which were separated to give a pure sample of odorine.

The optical rotations of naturally occurring odorine and dihydroodorine were compared with those of the synthetic samples, and this information, along with the measured optical rotation of the hydrolysis product 2 - methylbutanoic acid, enabled the absolute configuration of odorine to be determined.

RESULTS AND DISCUSSION

2.1 Synthesis of Dihydroodorine (114).

As outlined in the introduction, dihydroodorine (114) should be obtainable from the addition of 2 - butylmagnesium bromide to the isocyanate (115) and this reaction scheme was now investigated. The (115) isocyanate was prepared from L-proline (116) as shown in Scheme 14.



Scheme 14

Treatment of L - proline (116), in sodium hydroxide solution, with 3 - phenylpropanoyl chloride gave the optically active acid (117) in good yield. This acid was converted to the acyl azide (118) by treatment with ethyl chloroformate followed by the addition of sodium azide. The decomposition of the azide (118) to the isocyanate(115)

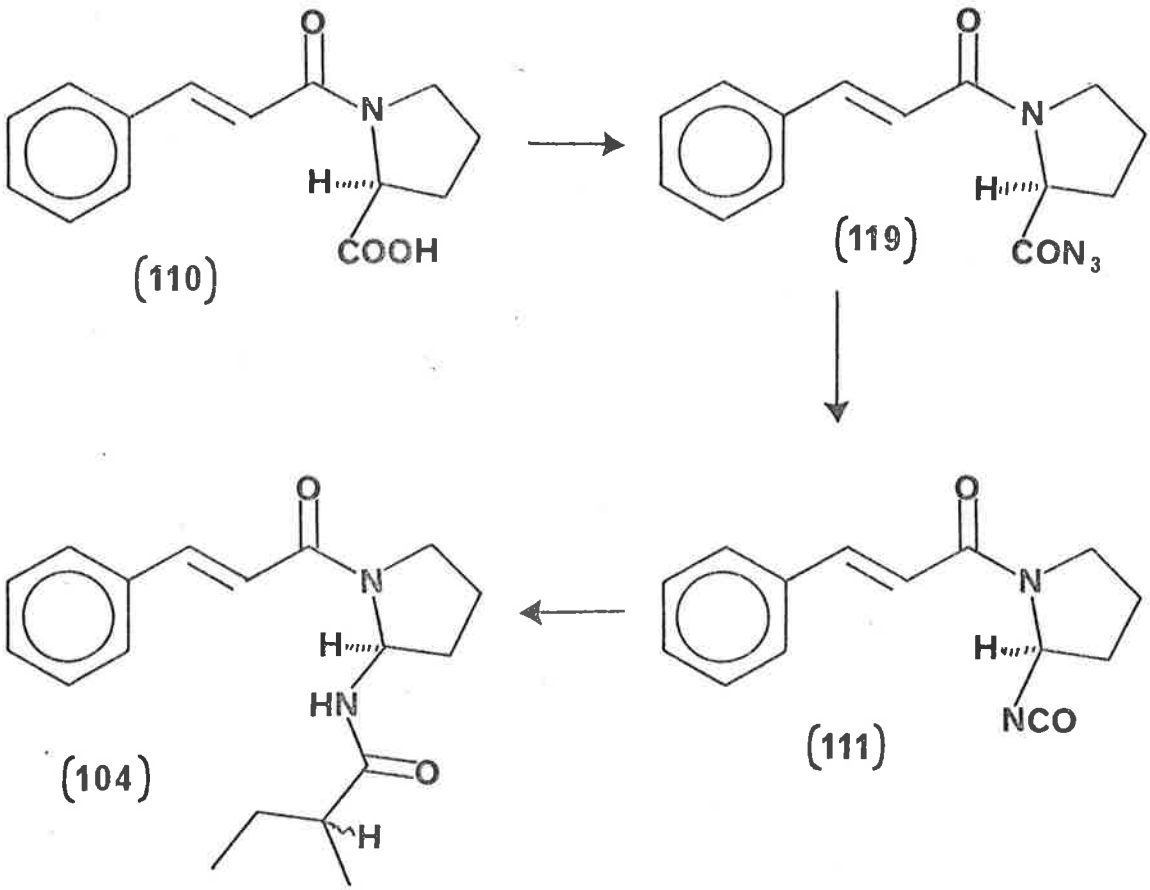
could be conveniently followed by infrared spectroscopy; the acyl azide showed a strong absorbtion at 2100 cm^{-1} while the isocyanate absorbed at 2220cm^{-1} . It was found that the acyl azide (118) was completely decomposed to the isocyanate (115) in 90 minutes in boiling tetrahydrofuran.

After an extensive investigation of reaction conditions, the treatment of the isocyanate (115) with 2 - butylmagnesium bromide afforded a mixture of the two diastereoisomers of dihydroodorine in good yield. This mixture of isomers proved to be extremely difficult to separate. It was possible to obtain a pure sample of epidihydroodorine by carefully repeated fractional recrystallisations, however dihydroodorine itself could not be isolated by this method. Pure samples of both dihydroodorine and epidihydroodorine were eventually obtained by the use of high pressure liquid chromatography. The assignment of the two diastereoisomers was made on the basis of comparison with an authentic sample. A sample of the synthetic dihydroodorine had spectral data and a melting point identical to an authentic sample of dihydroodorine, which was prepared by hydrogenation of odorine in ethyl acetate over platinum oxide.

2.2 Synthesis of Odorine (104).

Following the successful synthesis of dihydroodorine, attention was now directed to the synthesis of odorine itself. A previous attempt[82] at this synthesis had

failed, however after investigation of the reaction conditions this synthesis was accomplished by a similar route to that used in the synthesis of dihydroodorine, (Scheme 15).



Scheme 15

The optically active acid (110) was treated successively with ethyl chloroformate and sodium azide to give the acyl azide (119). This azide was heated in boiling tetrahydrofuran for 60 minutes to form the isocyanate (111), evidenced by the appearance of an absorbtion at 2160 cm^{-1} and the disappearance of the azide absorbtion at 2260 cm^{-1} in the infrared spectrum. Treatment of the isocyanate with one equivalent of 2 - butylmagnesium bromide afforded

odorine (104), in a mixture of two diastereoisomers, in moderate yield. These isomers were separated by high pressure liquid chromatography to give pure samples of the two isomers of odorine. One of the two isomers was shown to be identical to an authentic sample of odorine. Hydrogenation of the synthetic odorine yielded a compound identical to an authentic sample of dihydroodorine (114).

2.3 The stereochemistry of Odorine (104) and Dihydroodorine (114).

At this stage the absolute configuration of odorine could be determined since the stereochemistry of the synthetic compounds was readily obtainable. An authentic sample of odorine had a measured optical rotation of $+48^{o}$ compared to -20^{o} for a sample of synthetic odorine and -2^{o} for a sample of synthetic epiodorine. Similarly, an authentic sample of dihydroodorine had a measured rotation of -10^{o} compared with $+8^{o}$ for synthetic dihydroodorine and $+35^{o}$ for synthetic epidihydroodorine. From this it is obvious that the synthetic and authentic samples of odorine are enantiomers. The stereochemistry at C2' in synthetic odorine must therefore be S since the synthetic sequence started with L - proline which has the S configuration[83], and the Curtius rearrangement is known to proceed with retention of configuration. The configuration at C2' in naturally occurring odorine must therefore be R.

The configuration at C2 was determined from the measured

rotations of the 2 - methylbutanoic acids isolated from the acid hydrolysis of synthetic dihydroodorine and epidihydroodorine. The acid isolated from dihydroodorine had a negative rotation while that isolated from epidihydroodorine had a positive rotation. The negative rotation of the 2 - methylbutanoic acid isolated from synthetic dihydroodorine indicates the R configuration for the acid[84]. Naturally occurring odorine must therefore have the opposite S configuration at C2.

While dihydroodorine had been synthesised with quite high optical purity, it was noted that some racemisation had occurred in the synthesis of odorine, and attempts were therefore made to determine the source of the racemisation. This was found to be occurring mainly in the conversion of the acid (110) to the acyl azide (119), as shown by the following experiment. The acid(110) was treated with ethyl chloroformate and then sodium hydroxide, rather than sodium azide, was added to the solution to regenerate the starting acid. The recovered acid had an optical rotation of -136° compared with -212° for the starting acid, indicating that isomerisation was probably taking place in the mixed anhydride formed from the acid (110) and ethyl chloroformate. As a control experiment the acid (110) was also dissolved in sodium hydroxide solution and reisolated. The measured rotation of the acid recovered in this case was virtually identical to that of the starting acid.

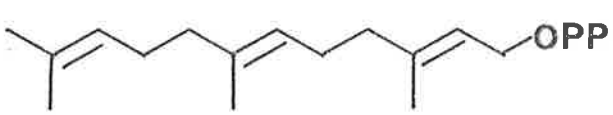
CHAPTER 3

The Structure of Scoparenonediol

INTRODUCTION

The terpenoids are among the most widespread and chemically interesting groups of natural products and have been studied since the earliest days of modern chemistry. The great variation in structure of these compounds and their frequent occurrence has made terpene research the centre of considerable attention[86-88].

It was not until the Biogenetic Isoprene Rule[89,90] and its later extensions[91,92] were proposed that the wide range of cyclic and acyclic structures was rationalised. Experimental evidence[93,94] has now shown that the sesquiterpenes are derived from farnesyl pyrophosphate (120), which is, in turn, produced by the sequential condensation of three molecules of isopentenyl pyrophosphate (121). The carbon skeleton of virtually all the sesquiterpenes can be derived by suitable cyclisations of farnesyl pyrophosphate (120).



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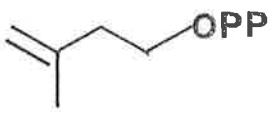

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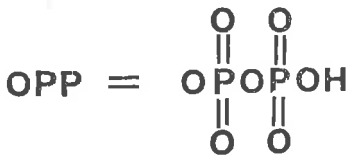
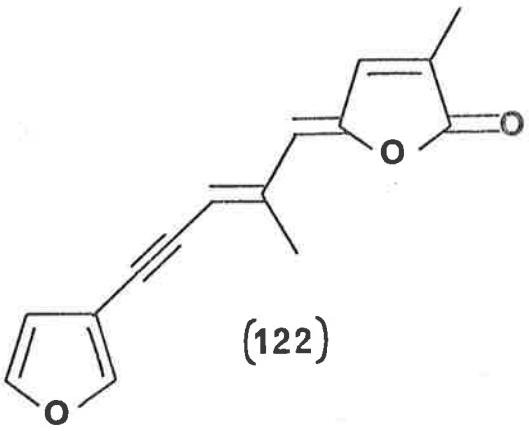


The investigation of plants of the Eremophila species has resulted in the isolation of a number of interesting compounds, the majority of them sesquiterpenes of various structural types. One such type is the furanosesquiterpenes, of which several have been

isolated[95-97]. The compound freelingyne (122)[98], isolated from Eremophila freelingii, is a typical example. Cyclised furanosequiterpenes have also been isolated. These include eremoacetal (123)[99], isolated from Eremophila rotundifolia, and alternifolenediol (124)[100], isolated from Eremophila alternifolia.



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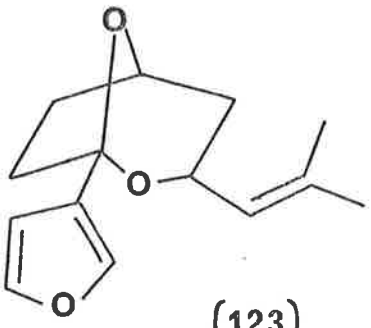

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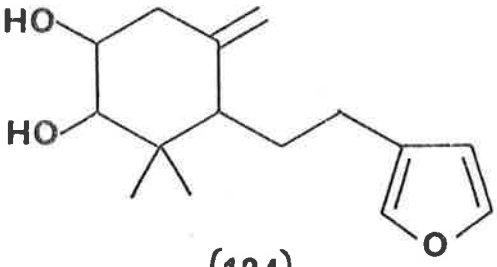
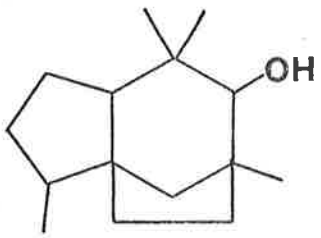


(124)

A tricyclic sesquiterpene (125)[101] has been isolated from Eremophila georgei. A number of sesquiterpenes related to eremophilone (126) are found in Eremophila mitchelli [102-104]. These compounds do not have an isoprenoid skeleton but are considered to be derived from the eudesmane skeleton by a methyl group migration[105]. An eremophilone dimer (127)[106] has also been isolated from the same plant. In the present work a sesquiterpene with a eudesmane

skeleton, named scoparenonediol (128), was isolated from Eremophila scoparia. This compound appears to be the first eudesmane derived terpenoid isolated from an Eremophila species.



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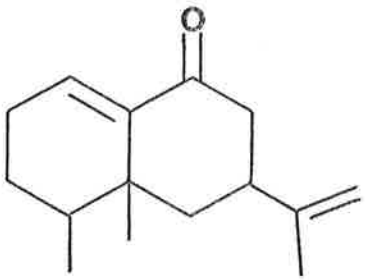

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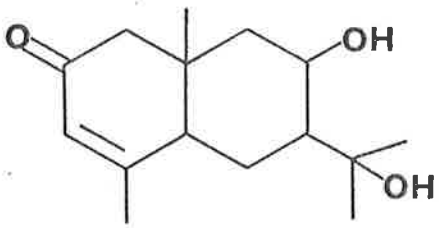

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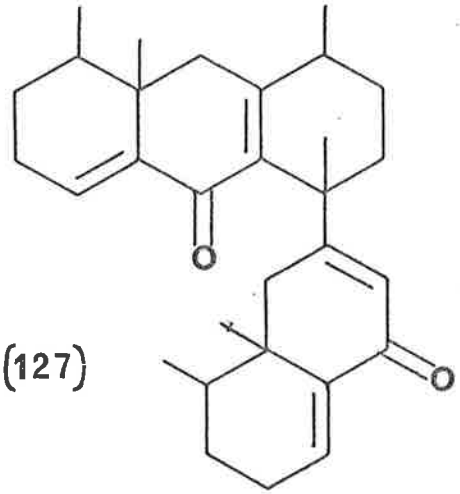
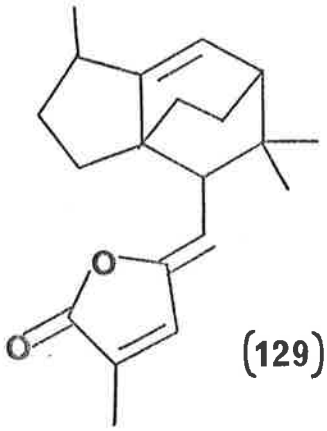


(127)

Several types of diterpenes have also been isolated from Eremophila species. These include eremolactone (129)[107] from Eremophila freelingii and dihydroserrulatic acid (130)[108], isolated from Eremophila serrulata. The unusual tricyclic diterpene (131)[109] has been isolated from Eremophila decipiens. Several macrocyclic diterpenes, for example (132), have been found in Eremophila clarkei and Eremophila georgei [110,111].



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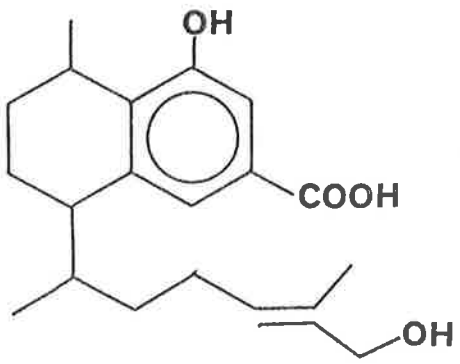

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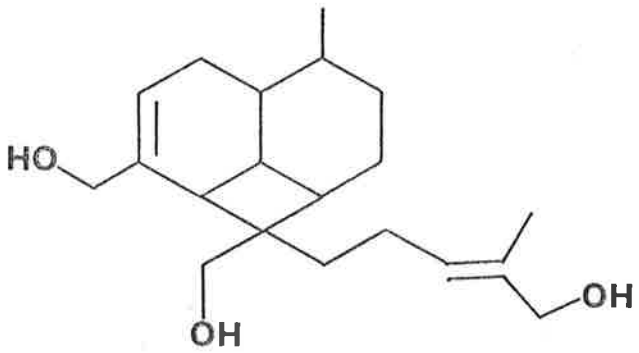

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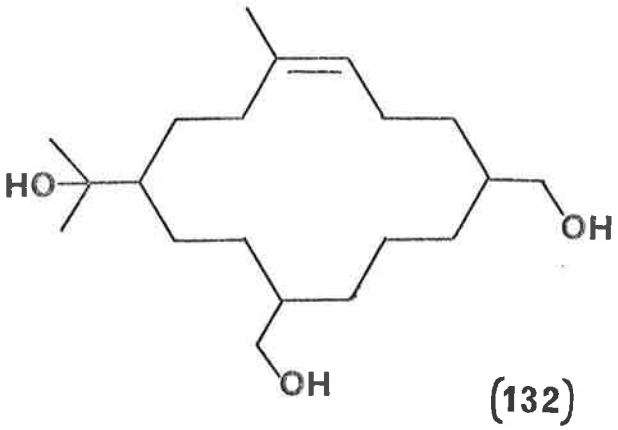
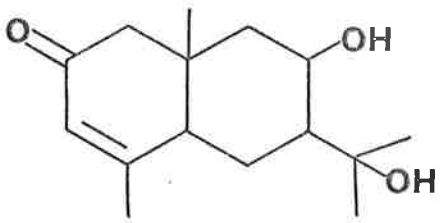


(132)

RESULTS AND DISCUSSION

Scoparenonediol (128) and the corresponding monoacetate (133) were isolated from the ether extract of the leaves of Eremophila scoparia by chromatography on silica gel. The mass spectrum of scoparenonediol indicated a molecular weight of 252, suggesting $C_{15}H_{24}O_3$ as the molecular formula. This was confirmed by an elemental analysis. The infrared spectrum indicated the presence of at least one hydroxyl group (3300 cm^{-1}) and an α , β - unsaturated carbonyl system (1660, 1620 cm^{-1}). The ultraviolet spectrum confirmed the presence of the α ,β - unsaturated carbonyl group by its absorbtion maximum of 243 nm, ε = 15,300. As the molecular formula requires the presence of two further double bond equivalents it is reasonable to assume that the compound has a bicyclic structure.



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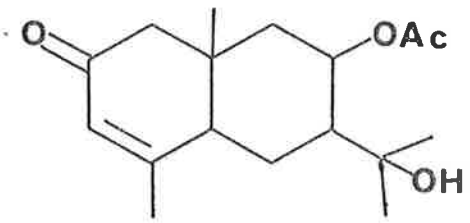
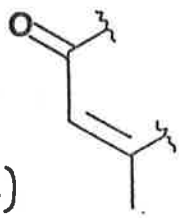


(133)

The ^1H NMR spectrum of scoparenonediol showed the presence of an olefinic proton adjacent to a carbonyl group (δ 5.9). Four methyl groups were also obvious (δ 0.9(s), 1.3(2), (s), 1.9(d)). One of the methyl groups (δ 1.9) was shown to be coupled to the olefinic proton (J = 2Hz) by spin - decoupling experiments, indicating that it was a substituent on the double bond, β to the carbonyl group. The ^{13}C NMR spectrum confirmed that the unsaturated carbon

β to the carbonyl group was fully substituted. Scoparenonediol must therefore contain the grouping (134).



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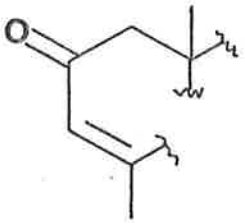
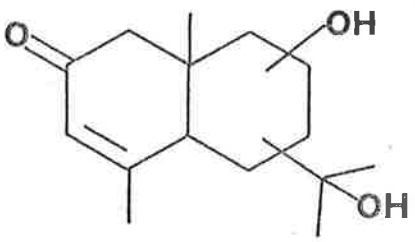


(135)

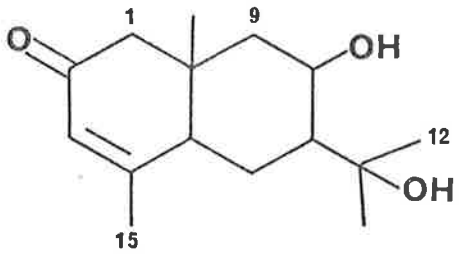
Furthermore the ^{1}H NMR spectrum also showed a sharp singlet absorbtion (δ 2.2) due to methylene protons α' to the carbonyl group, indicating that the β' carbon must be fully substituted. One possibility (135) is that this β' carbon bears the quaternary methyl group at δ 0.9. The two oxygen atoms, still to be accounted for must be present as a tertiary and a secondary hydroxyl group since there are two exchangeable protons in the ^{1}H NMR spectrum and only one proton on a carbon bearing oxygen.

The ^{13}C NMR spectrum also supports this conclusion since it shows one secondary and one tertiary carbon bearing oxygen at δ 67.7 and 74.3 respectively. The base peak in the mass spectrum of scoparenonediol was at m/e 59 and this, along with the presence of two equivalent methyl groups and a tertiary hydroxyl group, suggested the presence of an hydroxyisopropyl group. Assuming that the molecule has a decalin ring system, the structure thus far would be (136). Furthermore, the assumption that scoparenonediol is isoprenoid, with a regular head to tail linkage of isoprene units, would position the isopropyl group at C7. The ^{1}H NMR signal for the proton on carbon bearing oxygen is a

doublet of triplets. Therefore the only possible position for the hydroxyl group is at C8 (128).

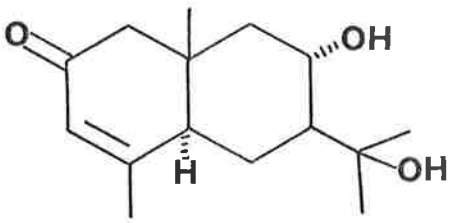


(136)

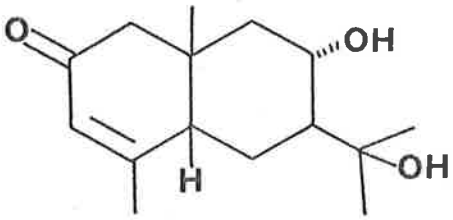


(128)

Examination of the coupling constants of H8 indicated that the hydroxyl and the hydroxyisopropyl group must be trans diequatorial since H8 showed diaxial coupling (J = 10Hz) to two protons and axial-equatorial coupling (J = 5Hz) to one proton[112]. Scoparenonediol was found to epimerise quite readily, when in solution, to another compound. Examination of the ^{1}H and ^{13}C NMR spectra of the two compounds revealed that the most significant change in each case was the chemical shift of the methyl group at the ring junction, changing from δ 0.9 to δ 1.2 in the ^{1}H spectrum and from δ 17.6 to δ 27.4 in the ^{13}C spectrum. The chemical shifts of δ 0.9 and δ 1.2 for this methyl group are typical of trans and cis fused eudesmanes respectively[113], and therefore the structure (128a) can now be assigned to scoparenonediol and structure (137) to its epimer. Acetylation of scoparenonediol produced a compound identical to the naturally occurring acetate (133).

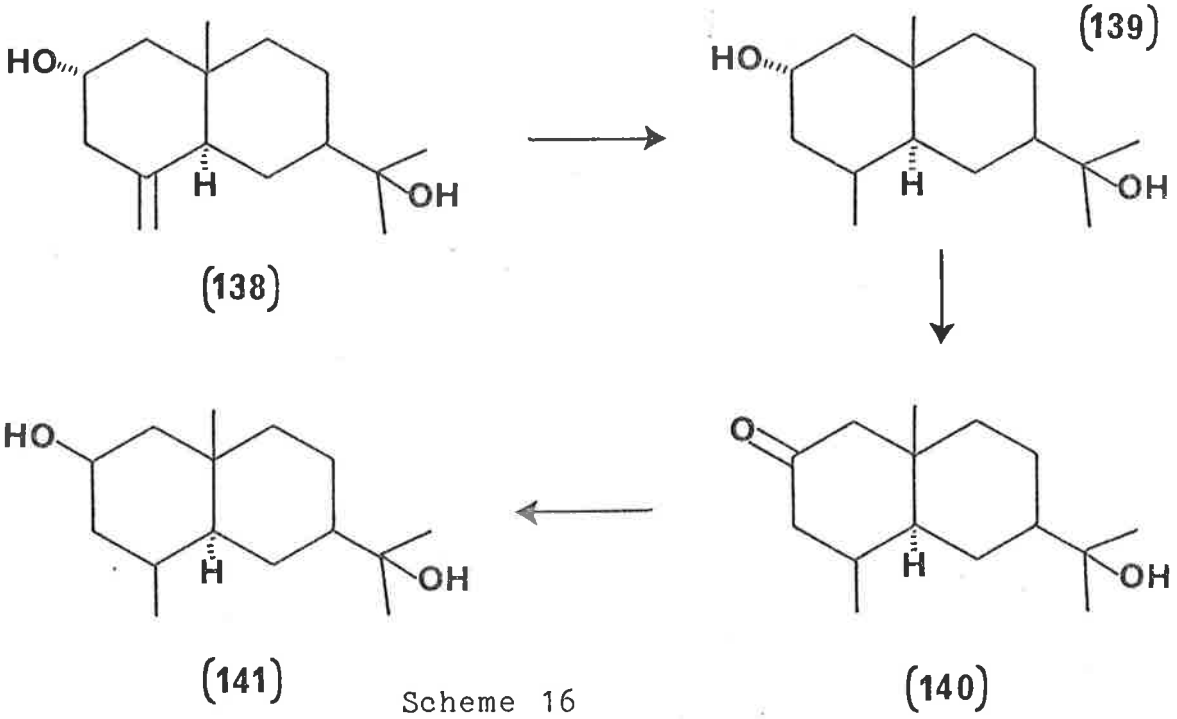


(128a)



(137)

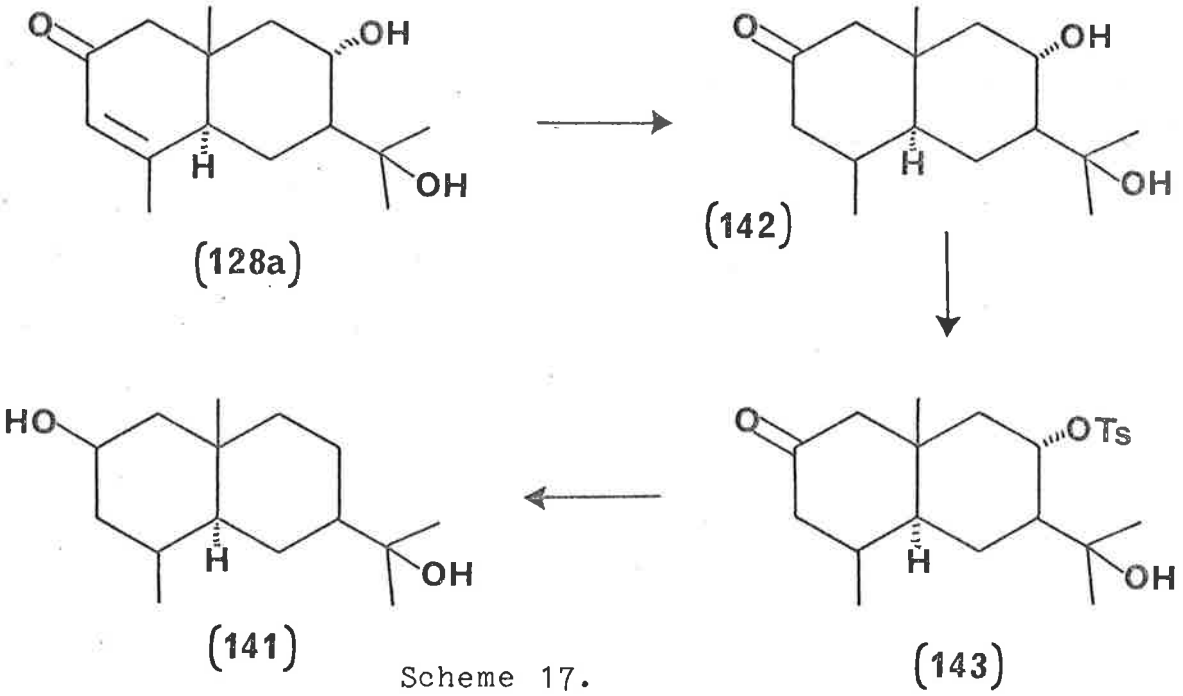
In order to confirm the structure and stereochemistry of scoparenonediol it was decided to convert it to the known compound epidihydropterocarpol (141)[114]. Epidihydropterocarpol was prepared from an authentic sample of pterocarpol (138) as shown in Scheme 16.



Scheme 16

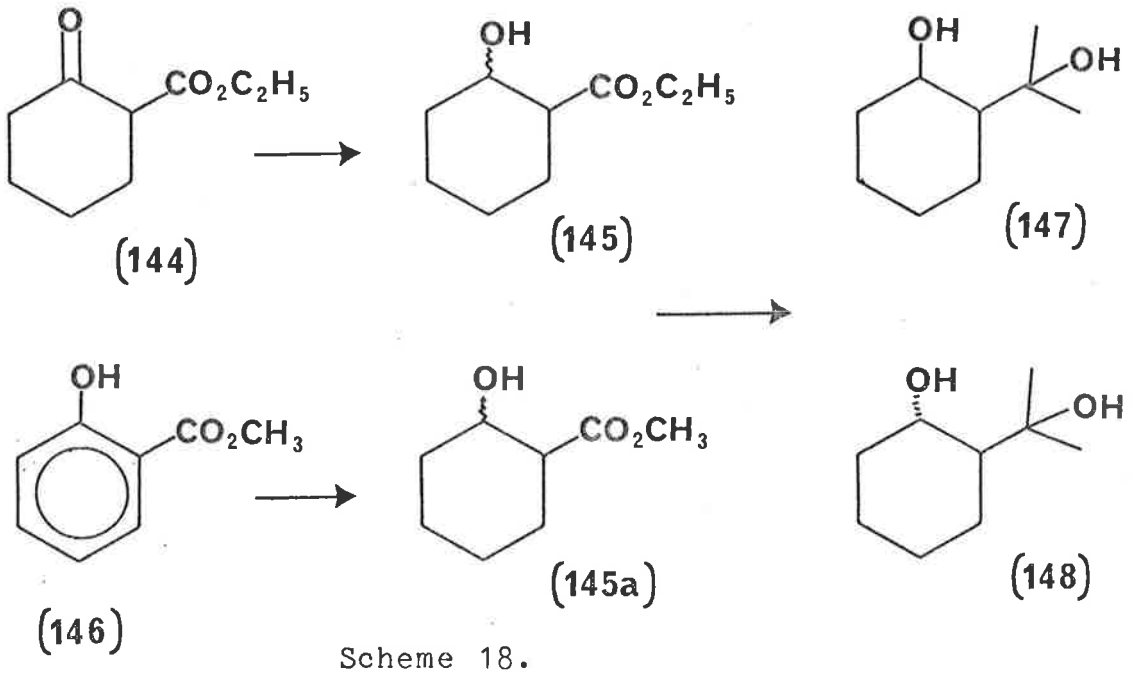
Pterocarpol (138)[114] was hydrogenated over palladised charcoal to give dihydropterocarpol (139). Excess Collins reagent converted dihydropterocarpol to the ketone (140) which afforded epidihydropterocarpol (141) upon treatment with lithium aluminium hydride.

Scoparenonediol (128a) could be converted to epidihydropterocarpol (141) by the route shown in Scheme 17.



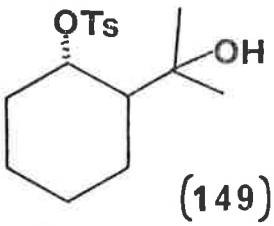
Scheme 17.

Hydrogenation of scoparenonediol (128a) over platinum oxide gave a good yield of dihydroscoparenonediol (142). Only one isomer was produced and this would be expected to have the stereochemistry shown, i.e. an axial methyl group at C4, due to addition of hydrogen to the less hindered side of the molecule. Treatment of dihydroscoparenonediol (142) with p-toluenesulphonyl chloride in pyridine afforded the p-toluenesulphonate ester (143) in good yield. It was anticipated that there could be difficulties with the reduction of the sulphonate ester (143), and since only a small amount of scoparenonediol was available the reduction was first investigated using a model compound, trans 2 - (2' - hydroxyisopropyl) - cyclohexanol (148). This compound was prepared by two methods (Scheme 18).

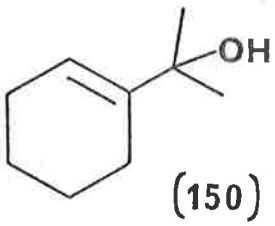


Scheme 18.

2-Carboethoxy - cyclohexanone (144) was reduced with sodium borohydride to give a mixture of cis and trans 2 - carboethoxy - cyclohexanols (145). A similar mixture of isomers (145a) was also prepared by the hydrogenation of methyl salicylate (146) over Raney nickel. Treatment of the mixture of hydroxy esters with excess methylmagnesium iodide afforded a mixture of cis and trans 2 - (2' - hydroxy - isopropyl) - cyclohexanols, (147) and (148). The isomers were separated by chromatography on silica gel and the pure trans isomer (148) was obtained as a crystalline solid. This diol was then esterified to the mono p-toluenesulphonate (149) by treatment with p - toluenesulphonyl chloride in pyridine.



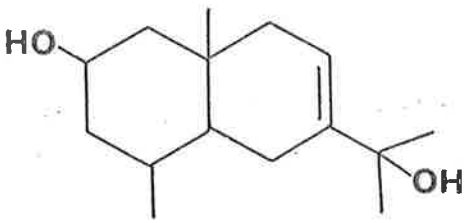
(149)



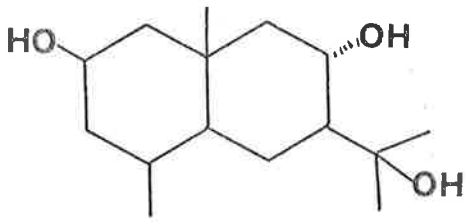
(150)

The treatment of the p - toluenesulphonate ester (149) with lithium aluminium hydride unexpectedly afforded the elimination product, 2'- hydroxyisopropyl - cyclohexene (150) in 77% yield; no reduction product could be detected. The same elimination product (150) was obtained when the reduction of (149) was attempted using sodium borohydride in dimethylsulphoxide. Two further reducing agents also investigated were a copper complex[122], formed from lithium trimethoxyaluminium hydride and cuprous iodide, and aluminium hydride. Both of these reagents also proved to be unsatisfactory in that the product (150) was again produced in the reaction.

At this stage it was decided to attempt the reduction of the p - toluenesulphonate ester of dihydroscoparenonediol (143) with lithium aluminium hydride since if any olefinic product were formed, hydrogenation of this compound would be expected to produce the required epidihydropterocarpol (141). When the reduction was carried out in boiling tetrahydrofuran, the elimination product (151) was produced, contaminated with another olefinic product from which it could not be separated. When the same reduction was carried out at -78° a mixture of the elimination product (151) and the triol (152) was obtained.



(151)



(152)

The formation of the triol (152) probably results from attack of the hydride reagent at sulphur rather than at carbon[115]. The hydroxyl group at C2 in (151) would be expected to be axial since the metal hydride is expected to attack from the less hindered side of the molecule[116]. The C2 hydroxyl group in epidihydropterocarpol (141) would also be axial for the same reason. Hydrogenation of the olefinic product (151) using platinum oxide in ether afforded epidihydropterocarpol (143) which had physical and spectral properties identical to the authentic sample prepared from pterocarpol (138). This confirms the structure (128a) originally assigned to scopareonediol.

EXPERIMENTAL

General

Melting points were determined using a Kofler hot-stage microscope and are uncorrected. Elemental analyses were performed by the Australian microanalytical Service, Melbourne.

Infrared spectra were recorded on either a Jasco IRA-1 or a Unicam SP200G spectrophotometer. Unless otherwise stated, spectra were recorded as Nujol mulls.

^{1}H Nuclear magnetic resonance (NMR) spectra were determined in deuterochloroform solution containing tetramethylsilane as an internal standard. Spectra were recorded on a Varian T60 spectrometer. Resonances are reported as singlet (s), broad singlet (br s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), doublet of triplets (dt) and multiplet (m).

^{13}C NMR spectra were determined in deuterochloroform solution containing tetramethylsilane as internal standard. Spectra were recorded on either a Bruker WP-80 spectrometer operating at 20.1 MHz or a Bruker HX90E spectrometer operating at 22.6 MHz.

Ultraviolet spectra were recorded on a Unicam SP800 spectrophotometer.

Mass spectra were recorded on either an Hitachi Perkin-Elmer RMU-7D spectrometer or an AEI-GEC MS 3074 high

resolution mass spectrometer. Accurate mass measurements were obtained from the latter instrument.

Optical rotations were measured on a Perkin-Elmer 141 polarimeter.

Preparative thin layer chromatography (TLC) was carried out on 20cm x 20cm glass plates coated with a 1:1 mixture of Merck Kieselgel G and HF_{254}.

High pressure liquid chromatography was carried out on a Spectra-Physics 3500 instrument equipped with an ultraviolet detector.

Solvents were purified by standard procedures[124]. Light petroleum refers to the fraction b.p. 60^{o} - 65^{o}. All organic extracts were dried over anhydrous magnesium sulphate unless otherwise stated.

CHAPTER 1

(Methylthio)carbonyl methylene -triphenylphosphorane (5)[20]

A suspension of methyltriphenyl phosphonium iodide (93gm, 250 mmol) and sodium amide (20gm, 500 mmol) in dry benzene (500ml) was stirred at room temperature under nitrogen for 8 hours. The precipitate was separated and the ammonia removed under reduced pressure to give a yellow solution of the ylid. Methyl S - methyl xanthate[56] (61gm, 500mmol)(7) was added to the solution and the mixture heated under reflux, with efficient stirring, under nitrogen for 12 hours. The precipitate was then filtered, washed with benzene, and dried to give (methylthio)carbonyl- methylene - triphenylphosphorane (62g, 72%). A small portion, recrystallised from ethyl acetate, had m.p. 218° - 220° (lit.[20] 220° - 221°). ^{1}H NMR δ2.27 (3H, s, $-SCH_3$), 3.62 (1H, d, J =22Hz, CHCOSMe), 7.3 - 7.9 (15H,m, aromatic H).

S - Methyl (E) - and (Z) - 3,4 - Dimethyl - 5 - oxo - 2, 5 - dihydrofuran - 2 - ylidenethanethioate (10) and (11)

A solution of dimethylmaleic anhydride (9) (1.26g, 10mmol) and (methylthio)carbonyl - methylene - triphenylphosphorane (5) (3.5g, 10mmol) in benzene (50ml) was heated under reflux for 24 hours. The solvent was removed and the residue chromatographed on silica gel with mixtures of light petroleum and ether. S - Methyl (E) - 3,4 - dimethyl - 5 - oxo - 2, 5 - dihydrofuran - 2 - ylidenethanethioate (10) (600mg, 30%) crystallised from light petroleum, m.p. 66° - 67° (Found: C,54.8; H,5.0 $C_9H_{10}O_3S$ requires C,54.6;

H,5.1%) ν_{max} 1770, 1665, 1620, 1610 cm^{-1}. ^1H NMR δ 1.97 (3H,br s, C4-Me) 2.27 (3H, d, J =1Hz, C3 - Me), 2.43 (3H, s, - SCH_3), 6.22 (1H, s, CHCOSMe) ^{13}C NMR δ 9.08 (C4-Me), 12.34(SMe), 13.07 (C3 - Me), 108.55, 131.91, 146.19, 155.50, 168.45, 187.45.

Further elution gave S - methyl (Z) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidenethanethioate (11) (1.0g,51%), m.p. 119°-120°, after recrystallisation from light petroleum. (Found : C,54.5; H,5.1; $C_9H_{10}O_3S$ requires C,54.6; H,5.1%) ν_{max} 1780, 1650, 1620, cm^{-1}. ^1H NMR δ 2.0 (3H,br s, C4-Me), 2.08(3H, d, J = 1Hz, C3-Me), 2.42 (3H,s,-SCH_3), 5.72 (1H,s, CHCOSMe). ^{13}C NMR δ 9.20 (C4-Me), 11.86(SMe), 102.86, 129.24, 147.40, 154.54, 168.57, 186.12.

S - Methyl (E) - 4 - Methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidenethanethioate (13) and S - Methyl (Z) - 3 - Methyl - 5 - oxo - 2,5 - dihydrofuran - 2 -ylidene - ethanethioate (14)

A solution of citraconic anhydride (12) (1.12g, 10mmol) and (methylthio)carbonyl - methylene - triphenylphosphorane (5) (3.5g, 10mmol) in benzene (50ml) was heated under reflux under a nitrogen atmosphere for 2 hours. After removal of solvent, chromatography on silica gel with mixtures of light petroleum and ether gave S - methyl (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidenethanethioate (13) (1.0g, 54%), m.p. 104°-105°, from light petroleum. (Found:C,52.1; H,4.5; C_8,H_8O_3S requires C,52.2; H,4.4%)

ν_{max} 1780,1660,1610 cm^{-1}. ^1H NMR δ 2.12 (3H,d, $\underline{J}$ =1.5 Hz, C4-Me), 2.47 (3H, s, $-SCH_3$), 6.13 (1H,s, CHCOSMe), 7.98 (1H, q, $\underline{J}$ =1.5Hz, H3).

Further elution gave S - methyl ($\underline{Z}$) - 3 - methyl - 5 - oxo -2,5 - dihydrofuran - 2 - ylidenethanethioate (14), which on recrystallisation from light petroleum gave colourless needles (50mg, 3%), m.p. 112^o-114^o. (Found: C,51.9; H,4.5, $C_8H_8O_3S$ requires C,52.2; H,4.4%) ν_{max} 1790, 1760, 1650, 1620cm^{-1}. ^1H NMR δ 2.23 (3H, d, $\underline{J}$ =1.5Hz, C3-Me), 2.43(3H, s, $-SCH_3$), 5.73(1H, s, CHCOSMe), 6.23(1H, br s, H4).

S - Methyl (E) - 5 - Oxotetrahydrofuran - 2 - ylidene - ethanethioate (19)

A solution of (methylthio)carbonyl - methylenetriphenyl - phosphorane (5) (3.5g, 10mmol) and succinic anhydride (18) (1.0 g, 10mmol) in benzene (50 ml) was heated under reflux for 24 hours. The solvent was removed and the residue chromatographed on silica gel with mixtures of light petroleum and ether. S - Methyl ($\underline{E}$) - 5 - oxo - tetrahydrofuran - 2 - ylidenethanethioate (19), (700mg, 41%) crystallised from light petroleum, m.p. 149^o-150^o. (Found C,48.9; H,4.8: $C_7H_8O_3S$ requires C,48.8; H,4.7%). ν_{max} 1820, 1660, 1610 cm^{-1}. ^1H NMR δ 2.4 (3H, s, $-SCH_3$), 2.5 - 3.0 (2H, m, $[H4]_2$), 3.2 - 3.7 (2H, m, $[H3]_2$), 6.13 (1H, t, $\underline{J}$ =2.5 Hz, CHCOSMe).

1 - (Methylthio)carbonyl -ethylidene- triphenylphosphorane (21)

1. To a solution of (methylthio)carbonyl - methylene - triphenylphosphorane (5), (17.5g, 50mmol) in dichloromethane (100ml) was added, all at once, methyl iodide (35g, 250mmol) and the solution heated under reflux for one hour. The solution was cooled and then shaken with 10% aqueous sodium hydroxide solution (100ml), the organic layer separated, dried, and the solvent removed. The residue was chromatographed on alumina, eluting with light petroleum/ether mixtures, to give 1 - (methylthio)carbonyl - ethylidene - triphenylphosphorane (21), (6.5g, 36%) m.p. 195° - 200°, after recrystallisation from ethyl acetate.

2. A suspension of ethyltriphenyl phosphonium iodide (38g, 100mmol) and sodium amide (7.8g, 200mmol) in dry benzene (250ml) was stirred under nitrogen for 8 hours at room temperature. Methyl S-methyl xanthate (7)[56], (25g, 200mmol) was added to the solution, obtained by separation of the precipitate and removal of the ammonia under reduced pressure, and the solution heated under reflux, with stirring, for 12 hours under nitrogen. The solvent was removed and the resulting oil chromatographed on alumina to give 1 - (methylthio)carbonyl - ethylidenetriphenyl - phosphorane (21), (17.1g, 47%), m.p. 195° - 200°, after recrystallisation from ethyl acetate. (Found: C,72.9; H,5.7; $C_{22}H_{21}OPS$ requires C,72.5; H,5.8%). ν_{max} 1550cm^{-1}. ^{1}H NMR δ1.67 (3H,d, J = 14Hz, C-CH_3), 2.25 (3H, s, -SCH_3), 7.3 - 7.9 (15H, m, aromatic H).

S - Methyl (E) - and (Z) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate, (23) and (24)

A solution of dimethylmaleic anhydride (9), 1.2g, 10mmol) and 1 - (methylthio)carbonyl - ethylidenetriphenyl - phosphorane (21), (3.65g, 10mmol) in benzene (50ml) was heated under reflux for 48 hours. The solvent was removed and the residue chromatographed on silica gel with mixtures of light petroleum and ether. S - Methyl (E) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (23), (390mg, 44%) crystallised from light petroleum, m.p. 62.5° - 63.5°. (Found: C,56.7; H,5.7; $C_{10}H_{12}O_3S$ requires C,56.6; H,5.7%). ν_{max} 1760, 1660, 1620 cm^{-1}. ^1H NMR δ 1.93 (3H, br s, C4-Me), 2.07 (3H, br s, C3-Me), 2.23 (3H, s, C2' - Me), 2.47 (3H, s, SCH_3). ^{13}C NMR δ 8.71 (C4-Me), 12.34 (C2' - Me, -SMe), 16.34 (C3 - Me), 119.8, 128.27, 145.58, 148.12, 168.69, 194.23.

Further elution gave, after recrystallisation from light petroleum, S - methyl (Z) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (24), (460mg, 22%), m.p. 93° - 94°. (Found: C,56.6; H,5.7; $C_{10}H_{12}O_3S$ requires C,56.6; H,5.7%) ν_{max} 1775, 1620 cm^{-1}. ^1H NMR δ1.93 (3H, br s, C4 - Me), 2.20 (3H, s, C2' - Me), 2.25 (3H, br s, C3 - Me), 2.38 (3H, s, $-SCH_3$). ^{13}C NMR δ8.83 (C4 - Me); 12.34 (SCH_3), 14.16 (C3 - Me, C2' - Me), 117.75, 129.12, 146.55, 146.85, 168.21, 192.78.

Reaction of Citraconic Anhydride (12) with 1 - (Methylthio) carbonylethylidene - triphenylphosphorane (21)

A solution of citraconic anhydride (12), (1.12g, 10mmol) and 1 - (methylthio)carbonyl - ethylidenetriphenyl - phosphorane (21), (3.65g, 10mmol) in benzene (50ml) was heated under reflux under nitrogen for 8 hours. Chromatography of the residue, after removal of solvent, on silica gel with mixtures of light petroleum and ether gave, after recrystallisation from light petroleum, S - methyl (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (25), (1.15g, 58%), m.p. 71^{o} - 72^{o}. (Found: C,54.2; H,5.1; $C_9H_{10}O_3S$ requires C,54.6; H,5.1%) ν_{max} 1765, 1660, 1620 cm^{-1}. ^1H NMR δ 2.07 (3H, br s, C4 - Me), 2.25 (3H, s, C2' - Me), 2.42 (3H, s, $-SCH_3$), 7.9 (1H, q, J =1.5Hz, H3).

Further elution gave S - methyl (E) - 3 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (27), (50mg, 2.5%), m.p. 90^{o} - 91^{o}, from light petroleum. (Found: C,54.3; H,5.4; $C_9H_{10}O_3S$ requires C,54.6; H,5.1%) ν_{max} 1780, 1650, 1615 cm^{-1}. ^1H NMR δ 2.2 (3H, d, J = 1.5Hz, C3 - Me), 2.23 (3H, s, C2'-Me), 2.45 (3H, s, $-SCH_3$), 6.05 (1H, br s, H3).

Finally S - methyl (Z) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (26), (300mg, 15%) was eluted, m.p. 102^{o} - 103^{o}, after recrystallisation from light petroleum. (Found: C,54.6; H,5.2; $C_9H_{10}O_3S$ requires C,54.6; H,5.1%). ν_{max} 1790,

1640, 1610 cm^{-1}. ^1H NMR δ 2.13 (6H, s, C4-Me, C2'-Me), 2.42 (3H, s, $-SCH_3$), 7.52 (1H, br s, H3).

Ethyl (E) - and (Z) - 5 - Oxotetrahydrothiophene - 2 - ylideneacetate, (30) and (31)

A solution of ethoxycarbonylmethylene - triphenyl - phosphorane (29), (3.5g, 10mmol) and succinic thioanhydride (28)[23], (1.16g, 10mmol) in benzene (50mol) was heated under reflux for 16 hours. The solvent was removed and the residue chromatographed on silica gel. Elution with mixtures of light petroleum and ether gave ethyl (E) - 5 - oxotetrahydrothiophene - 2 - ylideneacetate (30), which was recrystallised from light petroleum to give a white crystalline solid (550mg, 29%), m.p. 41^o - 42^o. (Found: C,51.6; H,5.3. $C_8H_{10}O_3S$ requires C,51.6; H,5.4%) ν_{max} 1800, 1710 cm^{-1}. ^1H NMR δ 1.3 (3H, t, $C\underline{H}_3CH_2O$), 2.7 - 3.1 (2H, m, $[H4]_2$), 3.4 - 3.8 (2H, m, $[H3]_2$), 4.2 (2H, q, $CH_3C\underline{H}_2O$), 6.07 (1H, t, $\underline{J}$ =2.5Hz, $CHCO_2Et$).

Further elution gave ethyl (Z) - 5 - oxotetrahydrothiophene - 2 - ylideneacetate (31), (500mg, 27%), b.p. 85^o/0.1mm (heated block). (Found: C,51.8: H,5.7 $C_8H_{10}O_3S$ requires C,51.6; H,5.4%). ν_{max} 1730, 1690, 1610 cm^{-1}. ^1H NMR δ 1.3 (3H, t, $C\underline{H}_3CH_2$), 2.6 - 3.0 (2H,m, $[H4]_2$), 3.0 - 3.4 (2H, m, $[H3]_2$), 4.27 (2H, q, $CH_3C\underline{H}_2$), 6.17 (1H, t, $\underline{J}$ =1Hz, $CHCO_2Et$).

Ethyl (E) - and (Z) - 3 - Oxo - 1,3 - dihydroisobenzo - thiophene - 1 - ylideneacetate, (33) and (34)

Phthalic thioanhydride (32)[25] (1.64g, 10mmol) and ethoxycarbonylmethylene - triphenylphosphorane (29), (3.5g, 10mmol) in dichloromethane (50ml) were heated under reflux for 3 hours. Removal of the solvent and chromatography on silica gel, eluting with light petroleum/ether mixtures, afforded ethyl (E) - 3 - oxo - 1,3 - dihydroisobenzo - thiophene - 1 - ylideneacetate (33), (350mg, 11%) which crystallised from light petroleum, m.p. 62° - 63°. (Found: C,61.5, H,4.3, $C_{12}H_{10}O_3S$ requires C,61.5; H,4.3%) ν_{max} 1720, 1700, 1600 cm^{-1}. ^1H NMR δ 1.33 (3H, t, $C\underline{H}_3CH_2$), 4.27 (2H, q, $CH_3C\underline{H}_2$), 6.37 (1H, s, $CHCO_2Et$), 7.5 - 8.0 (3H, m, H4, H5, H6), 9.2 (1H, dd, J =2Hz, 6Hz, H7).

Further elution afforded ethyl (Z) - 3 - oxo - 1,3- dihydro - isobenzothiophene - 1 - ylideneacetate (34), (1.6g, 68%) which was recrystallised from light petroleum, m.p. 116° - 117°. (Found:C,61.7; H,4.5, $C_{12}H_{10}O_3$ requires C,61.5; H,4.3%) ν_{max} 1685, 1600 cm^{-1}. ^1H NMR δ 1.37 (3H,t, $C\underline{H}_3CH_2$), 4.37 (2H,q, $CH_3C\underline{H}_2$), 6.9 (1H,s, $CHCO_2Et$), 7.6 - 8.2 (4H, m, aromatic H).

Raney nickel

W-2 Raney nickel was prepared by the method of Mozingo[46].

3,4 - Dimethyl - 5 - methylidenefuran - 2(5H) - one (42)

1. A solution of S - methyl (E) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidenethanethioate (10), (100mg, 0.5mmol) in ethanol, containing Raney nickel (1g) in suspension, was heated under reflux for 2 hours. TLC indicated that all starting material had been consumed, however, no UV absorbing products could be detected.

2. A suspension of Raney nickel (2g) in acetone (10ml) was heated under reflux for 30 minutes. S - Methyl (E) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2-ylidene -ethanethioate (10), (100mg, 0.5mmol) in acetone (2ml) was then added and the solution heated under reflux for 18 hours. The Raney nickel was filtered off (celite), washed with acetone (3 x 20ml) and the solvent removed under reduced pressure. Preparative TLC (ether/light petroleum, 1:1) gave 3,4 dimethyl - 5 - methylidenefuran - 2(5H) - one (42), (47mg, 76%), m.p. 40° - 43° (lit[47] 41° - 45°), after recrystallisation from light petroleum. ν_{max} 1765, 1650 cm^{-1}. ^{1}H NMR δ 1.93 (3H, br s), 2.08 (3H, br s), 4.8 (1H,d, J = 3Hz), 5.07 (1H,d, J =3Hz).

3 - Methyl - 5 - methylidenefuran - 2(5H) - one (44)

S - Methyl (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidenethanethioate (100mg, 0.54mmol), (13) in acetone (2ml) was added to a stirred suspension of Raney nickel (2g) in acetone (10ml), which had been heated under reflux for 30

minutes. The solution was then heated for a further 18 hours, after which time the Raney nickel was filtered off and the solvent removed by distillation. Preparative TLC (ether/light petroleum, 1:1) gave 3 - methyl - 5 - methylidenefuran - 2(5H) - one (44), (29mg, 48%), b.p. 85°/25mm (heated block), (lit[48] 74°/10mm). ν_{max} 1770, 1655, 1625 cm^{-1}. ^1H NMR δ 2.0 (3H, d, $\underline{J}$ = 1.8Hz, C3-Me), 4.22 (1H,d, $\underline{J}$ = 2Hz), 5.07 (1H,d, $\underline{J}$ = 2Hz), 7.03 (1H,br s, H4).

(E) - 3 - Methyl - 5(1' - methylthioethylidene) - furan - 2(5H) - one (63)

S - Methyl ($\underline{E}$) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2-ylidenethanethioate (13), (100mg, 0.54mmol) in acetone (2ml) was added to a stirred suspension of Raney nickel (1g), in acetone (10ml) which had previously been heated under reflux for 45 minutes. The solution was heated for a further 18 hours, the Raney nickel filtered off and the solvent removed by distillation. Preparative TLC (ether/light petroleum, 1:1) afforded starting material (15mg, 15%), 3 - methyl - 5 - methylidenefuran - 2(5H) - one (44), (18mg, 29%) and ($\underline{E}$) - 3 - methyl - 5(1'-methylthioethylidene) - furan - 2(5H) - one (63), (31mg, 37%), m.p. 94° - 96°, after recrystallisation from light petroleum. (Found: C,53.4; H,5.3; $C_7H_8O_2S$ requires C,53.9; H,5.2%) ν_{max} 1740, 1620, 1600 cm^{-1}, ^1H NMR δ 2.0 (3H,br s, C3-Me), 2.5 (3H, s,-SCH_3), 5.75 (1H, br s), 6.95 (1H, br s, H4).

Treatment of (E) - 3 - Methyl - 5 (1' - methylthio - ethylidene) furan - 2(5H) - one (63) with Raney nickel.

A suspension of Raney nickel (500mg) in acetone (3ml) was heated under reflux for 30 minutes. (E) - 3 -methyl - 5(1' - methylthioethylidene) - furan - 2(5H) - one (63), (25mg) in acetone (0.5ml) was then added and the solution heated under reflux for 14 hours. Preparative TLC (ether/light petroleum, 1:1), after removal of the Raney nickel, gave 3 - methyl - 5 - methylidenefuran - 2(5H) - one (44), 15mg, 84%).

Treatment of S - Methyl (E) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (23) with Raney nickel.

S - Methyl (E) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (23), (100mg, 0.47mmol) in acetone (2ml) was added to a stirred suspension of Raney nickel (2g) in acetone (10ml) which had been heated under reflux for 30 minutes. Heating was continued for a further 18 hours, after which time the Raney nickel was removed by filtration (celite) and the acetone distilled off. Preparative TLC (ether/light petroleum, 1:1) yielded four products:

(Z) - 3,4 - Dimethyl - 5 - ethylidenefuran - 2(5H) - one (45), (30mg, 0,24mmol, 51%), b.p. $70^{o}/1mm$ (heated block) (lit[12] $58^{o}/0.35mm$). ν_{max} 1760, 1680, 1645 cm^{-1}.

^{1}H NMR δ 1.87 (3H, br s), 2.02 (3H, br s), 1.95 (3H, d, J =7Hz), 5.23 (1H, q, J =7Hz).

(E) - 3,4 - Dimethyl - 5 - ethylidenefuran - 2(5H) - one (46), (7mg, 0.056mmol, 12%), b.p. 70°/1mm (heated block). (Found: C,69.2; H,7.2%, $C_8H_{10}O_2$ requires C,69.6; H,7.3%). ν_{max} 1755, 1660, 1630 cm^{-1}. ^1H NMR δ 1.95 (3H, br s), 2.02 (3H, d, J =7Hz), 2.28 (3H, br s), 5.75 (1H, q, J = 7Hz)

(Probably) (E) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanal (47), (11mg, 0.66mmol, 14%), b.p. 80°/0.1mm (heated block). (Found M^+ at m/e 166.063, $C_9H_{10}O_3$ requires M^+ at m/e 166.063). ν_{max} 1770, 1670, 1620 cm^{-1}. ^1H NMR δ 2.07 (6H, br s), 2.33 (3H, br s), 10.47 (1H,s).

(Probably) (Z) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanal (48), (12mg, 0.072mmol, 15%), m.p. 137° - 138°, after recrystallisation from light petroleum. (Found:C,64.9; H,6.2%; $C_9H_{10}O_3$ requires C,65.1; H,6.1%). ν_{max} 1770, 1665, 1620 cm^{-1}. ^1H NMR δ 2.07 (6H,br s), 2.23 (3H,br s), 10.42 (1H,s).

Treatment of S - Methyl (Z) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (24) with Raney nickel.

The reaction of S - methyl (Z) - 3,4 - dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (24), (100mg, 0.47mmol) with Raney nickel (2g) under conditions identical to those described for the (E) isomer, gave the following four products:

(Z) - 3,4 - Dimethyl - 5 - ethylidenefuran - 2(5H) -

one (45), (6mg, 0.05mmol, 11%).

(E) - 3,4 - Dimethyl - 5 - ethylidenefuran - 2(5H) - one (46), (38mg, 0.3mmol, 64%).

(E) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 ylidene - 2' - propanal (47), (8mg, 0.05mmol, 11%).

(Z) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 ylidene - 2' - propanal (48), (8mg, 0.05mmol, 11%).

Treatment of (E) - and (Z) - 3,4 - Dimethyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2'- propanal, (47) and (48), with Raney nickel.

The mixture of aldehydes, (47) and (48), (50mg) in acetone (1ml) was added to a stirred suspension of Raney nickel (1g) in acetone (10ml) which had previously been heated under reflux for 30 minutes. The solution was then heated under reflux for a further 14 hours. The Raney nickel was filtered off (celite) and the solvent removed under reduced pressure. Preparative TLC (ether/light petroleum, 3:1) gave (E) and (Z) - 3,4 - dimethyl - 5 - (1' - hydroxymethyl - ethylidene)furan - 2(5H) - one, (60) and (61), (47mg,94%) which could not be separated, b.p. 90^{o}/0.1mm (heated block) (Found: C,64.1; H,7.5% $C_9H_{12}O_3$ requires C,64.3; H,7.2%). ν_{max} 3400, 1740, 1660, 1620 cm^{-1}. ^1H NMR δ 1.88 (3H, br s), 2.1 (3H, br s), 2.25 (3H, br s), 2.33 (1H, br, D_2O exch), 4.38 (2H,s).

Treatment of S - Methyl (E) - 4 - Methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (25) with Raney nickel.

1. A stirred suspension of Raney nickel (2g) in acetone (10ml) was heated under reflux for 30 minutes. S - Methyl (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (25), (100mg, 0.5mmol) in acetone (2ml) was then added and the solution heated for a further 14 hours. The Raney nickel was then filtered off and the solvent removed by distillation. Preparative TLC (ether/light petroleum, 1:1) afforded two products: (Z) - 3 - methyl - 5 - ethylidenefuran - 2(5H) - one (49)[11], b.p. 60°/1.5mm (heated block), m.p. 36° - 38°, (55mg, 0.44mmol, 89%). ν_{max} 1760, 1685, 1625 cm^{-1}, and (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanal (50), (4mg, 0.026mmol, 5%), m.p. 104° - 105° (light petroleum). (Found: C,63.0; H,5.3% $C_8H_8O_3$ requires C,63.2; H,5.3%). ν_{max} 1775, 1670, 1645 cm^{-1}. ^1H NMR δ 2.02 (3H,s), 2.15 (3H, br s), 7.77 (1H,q, J =2Hz), 10.12 (1H,s).

2. S- Methyl (E) - 4 -methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' propanethioate (25), (300mg, 1.52mmol) was treated with Raney nickel (4.5g) under conditions identical to those used previously. Preparative TLC yielded four products : starting material (69mg, 0.35mmol, 23%); (Z) - 3 - methyl - 5 - ethylidenefuran - 2(5H) - one (49), (65mg, 0.52mmol, 34%): (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanal (50), (15mg,

0.1mmol, 6%) and (E) - 3 - methyl - 5 - (1' - methylthio - ethylidene) - furan - 2(5H) - one (62), (80mg, 0.47mmol, 31%), b.p. 80%/1mm (heated block), (Found M^+ at m/e 170.041; $C_8H_{10}O_2S$ requires M^+ at m/e 170.040). ν_{max} 1760, 1615 cm^{-1}. ^1H NMR δ 2.0 (3H, br s, C3 - Me), 2.23 (3H, s, C1' - Me), 2.32 (3H, s, - SCH_3), 7.53 (1H, br s, H4).

(Z) - 3 - Methyl - 5 - ethylidenefuran - 2(5H) - one (49).

(E) - 3 - Methyl - 5(1' - methylthioethylidene) - furan -2(5H) - one (62), (25mg) in acetone (0.5ml) was added to a stirred suspension of Raney nickel (500mg) in acetone (3ml) which had previously been heated under reflux for 30 minutes. After a further 14 hours heating, the Raney nickel was filtered off and the solvent removed by distillation. Preparative TLC (ether/light petroleum, 1:1) gave (Z) - 3 - methyl - 5 - ethylidenefuran - 2(5H) - one (49), (15mg), 83%).

Treatment of S - Methyl (Z) - 4 - Methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (26) with Raney Nickel.

A suspension of Raney nickel (2g) in acetone (10ml) was heated under reflux for 30 minutes. S - Methyl (Z) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (26), (100mg, 0.5mmol) in acetone (2ml) was then added and the solution heated under reflux for 18 hours. The nickel was then filtered off (celite) and the

acetone removed by distillation. Preparative TLC afforded three products : (Z) - 3 - methyl - 5 - ethylidenefuran - 2(5H) - one (49), (12mg, 0.097mmol, 19%) ; (E) - 4 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanal (50), (10mg, 0.066mmol, 13%), and (E) - 3 - methyl - 5 - ethylidenefuran - 2(5H) - one (51), (33mg, 0.27mmol, 54%), b.p. 60^{o}/2mm (heated block). (Found: M^{+} at m/e 124.053; $C_7H_8O_2$ requires M^{+} at m/e 124.052). ν_{max} 1760, 1675, 1625 cm^{-1}. ^{1}H NMR δ1.9 (3H, d, J =8Hz), 2.07(3H, d, J =1Hz), 5.67(1H, q, J = 8Hz), 7.32(1H, br s).

(Z) - 4 - Methyl - 5 - ethylidenefuran - 2(5H) - one (52)

S - Methyl (E) - 3 - methyl - 5 - oxo - 2,5 - dihydrofuran - 2 - ylidene - 2' - propanethioate (27), (20mg) was treated with Raney nickel (400mg) in acetone (2ml) under the usual conditions. Preparative TLC (ether/light petroleum, 1:1) gave a mixture of compounds which contained, by NMR, (Z) - 4 - methyl - 5 - ethylidenefuran - 2(5H) - one (52)[11]. This mixture was not further purified.

5- Methylidene - tetrahydrofuran - 2 - one (64)

S - Methyl (E) - 5 - oxotetrahydrofuran - 2 - ylidene - ethanethioate (19), (300mg, 1.74mmol) in acetone (2ml) was added to a strirred suspension of Raney nickel (6g) in acetone (15ml) which had previously been heated under reflux for 30 minutes. After a further 14 hours of heating under reflux, the Raney nickel was filtered off and the solvent removed by distillation. Preparative TLC (ether/light

petroleum, 1:1) gave 5 - methylidene - tetrahydrofuran - 2 - one (64), (20mg, 0.2mmol, 12%), b.p. 80°/22mm (heated block), (lit[53] 80°/17mm). ν_{max} 1810, 1675 cm^{-1}. ^1H NMR δ2.4 - 3.1 (4H, broad), 4.28 (1H, br), 4.73 (1H, br).

Treatment of Ethyl (Z) - 5 - Oxotetrahydrothiophene - 2 - ylideneacetate (31) with Raney nickel.

Ethyl (Z) - 5 - oxotetrahydrothiophene - 2 - ylidene - acetate (31), (100mg, 0.54mmol) in acetone (2ml) was added to a stirred suspension of Raney nickel (3g), in acetone (15ml) which had previously been heated under reflux for 20 minutes. Heating was continued for 48 hours, after which time the nickel was filtered off and the acetone removed by distillation. Preparative TLC (ether/light petroleum, 1:1) gave a product (36mg) which NMR indicated was a mixture of starting material and ethyl (E) - 6 - oxohex-2-enoate (65), ^1H NMR δ 5.88 (d, J =16Hz), 6.08 (t, J =1.5Hz), 7.1 (m), 10.02 (br s). As these two compounds could not be separated, the mixture was dissolved in deuterochloroform (0.5ml) in a NMR tube and ethoxycarbonylmethylene - triphenylphosphorane (29), (40mg) added to the solution. After 60 minutes at 35°, ^1H NMR indicated that the reaction was complete. Preparative TLC (ether/light petroleum), 1:1) gave starting material (20mg, 20%) and diethyl (E,E) octa - 2,6 - dienoate (66), (18mg, 0.08mmol, 15%), b.p. 85°/0.1mm (heated block), (lit[54] 102°/0.2mm). ν_{max} 1715, 1665 cm^{-1}. ^1H NMR δ 1.32 (6H, t, J =7Hz), 2.37 (4H, m), 4.18 (4H, q, J =7Hz), 5.83

(2H, br d, J = 16Hz), 7.0 (2H,m).

Treatment of (Z) - 3 - Oxo - 1,3 - dihydroisobenzo - thiophene - 1 - ylideneacetate (34) with Raney nickel.

A stirred suspension of Raney nickel (4g) in acetone (15ml) was heated under reflux for 30 minutes. (Z) - 3 - oxo - 1,3 - dihydro - isobenzothiophene - 1 - ylideneacetate (34), (200mg, 0.85mmol) in acetone (2ml) was then added and the solution heated for a further 24 hours. The Raney nickel was then filtered off and the solvent removed under reduced pressure. Preparative TLC (ether/light petroleum, 3:2) gave as the major product a 2:1 mixture of ethyl cinnamate (67) and ethyl 3 - phenylpropanoate (68), (80mg, 0.45mmol, 54%) which could not be separated. Also isolated were starting material (75mg, 38%), and a mixture of ethyl 3 - (2' - hydroxymethylphenyl) propenoate (69) and ethyl 3 - (2' - hydroxymethylphenyl) propanoate (70), (25mg, 0.12mmol, 14%), b.p. 110°/0.1mm (heated block), in the ratio 2:1 which could not be separated. (Found M^+ at m/e 206.095; $C_{12}H_{14}O_3$ requires M^+ at m/e 206.094; and M^+ at m/e 208.110; $C_{12}H_{16}O_3$ requires M^+ at m/e 208.110. ν_{max} 3400, 1710, 1690, 1635 cm^{-1}. ^1H NMR δ 1.30 (t, J =7Hz), 2.0 (br, D_2O exch), 2.83 (m), 4.23 (q, J =7Hz), 4.7 (s), 4.82 (s), 6.37 (d, J = 16Hz), 7.2 - 7.8 (m, aromatic H), 8.02 (d, J = 16Hz).

S - Methyl (E) - 3 - Phenylpropenethioate (71)

A solution of benzaldehyde (1.06g, 10mmol) and

(methylthio)carbonyl - methylene - triphenylphosphorane (5), (3.5g, 10mmol) in dichloromethane (50ml) was heated under reflux for 14 hours. The solvent was removed under reduced pressure and the residue chromatographed on silica gel, eluting with mixtures of light petroleum and ether. S - Methyl (E) - 3 - phenylpropenethioate (71), (1.48g, 83%) was obtained as yellow needles, m.p. 47° - 49° (light petroleum), (lit[55] 42° - 47°). ^{1}H NMR δ 2.38 (3H, s, SCH_3), 6.6 (1H, d, J =16Hz, H2), 7.1 - 7.6 (5H,m, aromatic H), 7.52 (1H, d, J = 16Hz, H3).

Treatment of S - Methyl (E) - 3 - Phenylpropenethioate (71) with Raney nickel.

A suspension of Raney nickel (2g) in acetone (10ml) was heated under reflux for 30 minutes. S - Methyl (E) - 3 - phenylpropenethioate (71), (100mg, 0.56mmol) in acetone (1ml) was added and the solution heated under reflux for 24 hours. The nickel was then filtered off and the acetone removed by distillation. Preparative TLC (ether/light petroleum 1:1) gave starting material (25mg, 25%) and cinnamaldehyde (72), (25mg, 0.19mmol, 34%). ^{1}H NMR δ 6.69 (1H, dd, J =16Hz, 7Hz), 7.5 (5H,m), 7.5 (1H, d, J =16Hz), as the only detectable product.

Ethyl (E) - 5 - Oxotetrahydrofuran - 2 - ylideneacetate (20)

The enol-lactone (20) was prepared from succinic anhydride (18) and ethoxycarbonylmethylene - triphenylphosphorane (29) in 59% yield, m.p. 94° - 96° (lit[14] 94° - 96°).

Diethyl (E,E) - and (Z,E) - 3,6 - Epoxyocta - 2,6 - dienoate (70) and (77)

Ethyl (E) - 5 - oxotetrahydrofuran - 2 - ylideneacetate (20), (150mg), and ethoxycarbonylmethylene - triphenylphosphorane (29), 307mg), were dissolved in carbon tetrachloride (0.5ml) and allowed to stand at room temperature for 7 days. Preparative TLC (ether/light petroleum, 3:1) gave two products. Diethyl (E,E) - 3,6 - epoxyocta - 2,6 - dienoate (76) (75mg, 35%) crystallised from light petroleum as colourless crystals, m.p. 120° - 121° (Found: C, 60.2; H, 6.6% $C_{12}H_{15}O_5$ requires C, 60.0; H, 6.7%). ν_{max} 1710, 1680, 1640 cm^{-1}. ^1H NMR δ 1.3 (6H, t, 2X $OCH_2\underline{CH_3}$), 3.3 (4H, s, $CH_2\underline{CH_2}$), 4.2 (4H, q, 2x $OCH_2\underline{CH_3}$), 5.6 (2H, s, H2 and H7).
Diethyl (Z,E) - 3,6 - epoxyocta - 2,6 - dienoate (77), (31mg, 15%) was recrystallised from light petroleum, m.p. 50° - 51° (Found: C,60.4; H,6.5% $C_{12}H_{16}O_5$ requires C,60.0; H,6.7%). ν_{max} 1710, 1640 cm^{-1}. ^1H NMR δ 1.3 (6H, t, 2x$OCH_2\underline{CH_3}$), 3.1 (4H, m, $CH_2\underline{CH_2}$), 4.2 (4H, q, 2x$OCH_2\underline{CH_3}$), 5.2 (1H, t, H2), 5.8 (1H, t, H7).

Acid isomerisation of Diethyl (E,E) - 3,6 - Epoxyocta - 2,6 - dienoate (76).

The diester (76) (240mg) was heated in chloroform solution, containing a few drops of trifluoroacetic acid, for 4 days at 75°. Isolation by preparative TLC

(ether/light petroleum, 3:1) gave diethyl furan - 2,5 - diacetate (10mg, 79%) (78).

The diester (78) was hydrolysed with sodium hydroxide (200mg) in water (5ml) under reflux for 16 hours. The solution was neutralised with concentrated HCl, acetone (100ml) added and the solid removed by filtration. After evaporation of the solvent furan - 2,5 - diacetic acid (79), (100mg, 69%) was recrystallised from ethanol/chloroform, m.p. 155^{o} - 156^{o} (lit[63] 154^{o} - 155^{o}).

Ethyl (E, 3aβ, 4α, 7α, 7aβ) - 3 - Oxoperhydro - 4,7 - epoxy isobenzofuran - 1 - ylideneacetate (80).

The enol-lactone (80) was prepared from endo - 3,6 - epoxyperhydrophthalic anhydride and ethoxycarbonylmethylene triphenylphosphorane (29) in 41% yield, m.p. 103^{o} - 104^{o} (lit[14] 104^{o}).

Reaction of Ethoxycarbonylmethylene - triphenylphosphorane (80) with Ethyl (E, 3aβ, 4α, 7α, 7aβ) - 3 - Oxoperhydro - 4,7 - epoxyisobenzofuran - 1 - ylideneacetate (29).

The enol-lactone (80), (239mg) and the phosphorane (29), (350mg) were dissolved in deuterochloroform in an NMR tube. After 16 hours at 60^{o} the ^{1}H NMR spectrum indicated that the reaction was complete. Preparative TLC (ether/light petroleum 3:1) gave two isomers. Diethyl (E,E, 3aβ, 4α, 7α, 7aβ) - perhydro - 4,7 - epoxyisobenzofuran - 1,3 - diylidenebisacetate (81), (220mg, 71%) crystallised from

chloroform/light petroleum as colourless crystals, m.p. 141° - 143° (Found: C, 62.5: H, 6.5% $C_{16}H_{20}O_6$ requires C, 62.3; H 6.5%). ν_{max} 1700, 1680, 1620 cm^{-1}, ^1H NMR δ 1.3 (6H, t, $OCH_2\underline{CH}_3$), 1.8 (4H, br s, CH_2CH_2), 3.7 (2H, s, H3a and H7a), 4.2 (4H, q, $OC\underline{H}_2CH_3$), 4.9 (2H, m, H4 and H7), 5.6 (2H, s, - $CHCO_2Et$). Diethyl (Z,E, 3aβ, 4α, 7α, 7aβ) - perhydro - 4,7 - epoxyisobenzofuran - 1,3 - diylidenebisacetate (82), (10mg, 4%) was isolated as crystals, m.p. 101° - 102°. (Found C, 62.0; H, 6.7%, $C_{16}H_{20}O_6$ requires C, 62.3; H, 6.5%). ν_{max} 1700, 1640 cm^{-1}. ^1H NMR δ 1.3 (6H, t, $OCH_2\underline{CH}_3$), 1.7 (4H, m, CH_2CH_2), 3.7 (2H, m, H3a and H7a), 4.2 (4H, q, $OC\underline{H}_2CH_3$), 4.6, 4.9(each 1H, m, H4 and H7), 5.2 (1H, d, (Z) $CHCO_2Et$), 5.7 (1H, d, (E) $CHCO_2Et$).

Reaction of Ethyl (E) - 5 - Oxotetrahydrofuran - 2 - ylideneacetate (20) with Methylcarbonylmethylene - triphenyl phosphorane (83).

The enol-lactone (20), (240mg) and the phosphorane (83), (450mg) were dissolved in deuterochloroform in an NMR tube. After heating at 90° for 6 hours no sign of the desired products could be detected by NMR.

Reaction of Ethyl (E, 3aβ, 4α, 7α, 7aβ) - 3 - Oxoperhydro - 4,7 - epoxyisobenzofuran - 1 - ylideneacetate (80) with Methylcarbonylmethylene - triphenylphosphorane (83).

The enol-lactone (80), (180mg) and the phosphorane (83), (240mg) were dissolved in deuterochloroform in an NMR tube.

No reaction was observed after the solution had been heated at 90° for 6 hours.

Reaction of (Z) - 4 - Methyl - 5 - (2'-oxopropylidene) furan - 2(5H) - one (84)[14] with Ethoxycarbonylmethylene - triphenylphosphorane (29).

A solution of the keto-lactone (84), (1.10g) and the phosphorane (29), (2.3g) in chloroform (15ml) was heated at 60° for 48 hours. Preparative TLC (ether/ light petroleum, 3:1) gave three products. Ethyl (2E,6Z) - 3,6 - epoxy - 5 - methyl - 8 - oxonona - 2,4,6 - trienoate (85), (350mg, 24%) crystallised from light petroleum, m.p. 119° - 121°. Found (C, 64.6; H, 6.0: $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.0%). ν_{max} 1710, 1640, 1620, cm^{-1}. λ_{max} 345nm ε19,100. ^1H NMR δ1.3 (3H, t, $OCH_2C\underline{H}_3$), 2.1 (3H, d, 5-CH_3), 2.5 (3H, s, $[H9]_3$), 4.2 (2H, q, $OC\underline{H}_2CH_3$), 5.5 (1H, s, H7), 5.7 (1H, s, H2), 7.5 (1H, br s, H4). ^{13}C NMR δ196 (ketone)δ166, (ester).

Ethyl 3 - methyl - 5 - oxo - 2 - (2' - oxopropylidene) cyclo - pent - 3 - enecarboxylate (86), (150mg, 10%) crystallised from light petroleum, m.p. 69° - 70°. (Found: C, 65.1; H, 6.6% $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%). ν_{max} 1735, 1720, 1690, 1610 cm^{-1}. λ_{max} 286nm, ε20,600. ^1H NMR δ1.3 (3H, t, $OCH_2C\underline{H}_3$), 2.3, 2.4 (each (3H, s, 3-CH_3 and $[H3']_3$), 4.25 (2H, q, $OC\underline{H}_2CH_3$), 4.3 (1H, s, exch., H1), 6.4, 6.5 (each 1H, br s, H4 and H1').
^{13}C NMR δ198, 197 (ketone), 169 (ester).

Ethyl (2Z,4Z) - 3 - methyl - 4 - (3' - methyl - 5' - oxo - 2',5' - dihydrofuran - 2' - ylidene) but - 2 - enoate (87),

(250mg, 17%) crystallised from light petroleum, m.p. 109° - 110°. (Found: C, 64.7; H, 6.4% $C_{12}H_{14}O_4$ requires C, 64.9; H, 6.3%). ν_{max} 1790, 1720, 1640, 1600, cm^{-1}. λ_{max} 322nm, ε 21800. ^1H NMR δ1.3 (3H, t, $OCH_2\underline{CH_3}$), 2.25, 2.3 (each 3H, d, 3-CH_3 and 3'-CH_3), 4.2 (2H, q, OCH_2CH_3), 5.8 6.0 (each 1H, br s, H4 and H2'), 7.5 (1H, s, H4'). ^{13}C NMR δ169, 166 (lactone and ester).

Reaction of (Z) - 3,4 - Dimethyl - 5 - (2' - oxopropylidene) - furan - 2(5H) - one (89)[14] with Ethoxycarbonylmethylene triphenylphosphorane (29).

A mixture of the enol-lactone (89), (900mg) and the phosphorane (29), (1.9g) in chloroform (15ml) was heated at 60° for 48 hours. Preparative TLC (ether/light petroleum, 3:1) gave three products. Ethyl (2Z,4Z) - 4 - (3',4' - dimethyl - 5' - oxo - 2', 5' - dihydrofuran - 2' - ylidene) - 3 - methylbut - 2 - enoate (90), (550mg, 43%) was recrystallised from light petroleum, m.p. 84° - 86°. (Found C, 66.3; H, 6.9% $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). ν_{max} 1790, 1720, 1650, 1600 cm^{-1} λ_{max} 322nm, ε 27800. ^1H NMR δ1.3 (3H, t, $OCH_2\underline{CH_3}$), 1.96, 2.13 (each 3H, s, 3' - CH_3 and 4' - CH_3), 2.32 (3H, d, $\underline{J}$ =1Hz, 3-CH_3), 4.2 (2H, q, OCH_2CH_3), 5.8 (1H, br s, H2), 7.42 (1H, s, H4). ^{13}C NMR δ169, 166 (lactone and ester). Ethyl (2Z,4Z) - 4 - (3', 4' - dimethyl - 5' - oxo - 2', 5' - dihydrofuran - 2' - ylidene) - 3 - methylbut - 2 - enoate (91), (130mg, 10%). (Found: C, 66.4; H, 6.9% $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). ν_{max} 1790, 1770, 1710, 1640, 1600 cm^{-1}. λ_{max} 322nm, ε 27400. ^1H NMR δ1.3 (3H, t

$OCH_2C\underline{H}_3$), 1.96, 2.08 (each 3H, s, 3'-CH_3 and 4' - CH_3), 2.53 (3H, d, $\underline{J}$ =1Hz, 3-CH_3), 4.2 (2H, q, $OC\underline{H}_2CH_3$), 5.36 (1H, s, H4), 6.1 (1H, br s, H2). ^{13}C NMR δ 170, 166 (lactone and ester).

Ethyl (2$\underline{Z}$, 6$\underline{Z}$) - 3,6 - epoxy - 4,5 - dimethyl - 8 - oxonona - 2,4,6 - trienoate (92), (75mg, 6%) was recrystallised from light petroleum, m.p. 230° - 232°. (Found: C, 66.4; H, 6.9% $C_{13}H_{16}O_4$ requires C, 66.1; H, 6.8%). ν_{max} 1700, 1660, 1640, 1620 cm^{-1}, λ_{max} 343, 360nm, ε16800, 15100. ^1H NMR δ1.3 (3H, t, $OCH_2C\underline{H}_3$), 1.97 (6H, s, 4-CH_3 and 5-CH_3) 2.67 (3H, s, $[H9]_3$), 4.26 (2H, q, $OC\underline{H}_2CH_3$), 5.3, 5.45 (each 1H, s, H2 and H7).

Reaction of Ethyl (E) - 5 - Oxo - 2,5 - dihydrofuran - 2 - ylideneacetate (93)[14] with Ethoxycarbonylmethylene - triphenylphosphorane (29).

The enol-lactone (93), (168mg) and phosphorane (29), (350mg) were dissolved in deuterochloroform in an NMR tube. After the tube had been allowed to stand at room temperature for two weeks and heated for a further two days the reaction mixture contained a large amount of tarry material and only a trace of the desired product could be detected by NMR.

Treatment of Butyrolactone (94) with Ethoxycarbonylmethylene triphenylphosphorane (29).

Butyrolactone (94), (86mg) and phosphorane (29), (350mg) were dissolved in deuterochloroform in an NMR tube. No reaction was observed, even after the solution had been

maintained at 90° for 6 hours.

Treatment of Isopropenyl Acetate (96) with Ethoxycarbonyl methylene - triphenylphosphorane (29).

Isopropenyl acetate (96), (100mg) and phosphorane (29), (350mg) were dissolved in deuterochloroform in an NMR tube, and maintained at 55° for two weeks. No reaction was observed.

Preparation of α-Angelica Lactone (95).

Laevulinic acid (4g) was distilled from polyphosphoric acid (100mg) to give a colourless liquid (3.0, 88%) b.p. 90° - 100°/13mm. ^{1}H NMR indicated that the product was a mixture of α-angelica lactone (b.p. lit[64] 49°/1.5mm) and β-angelica lactone in the ratio 2:1. ν_{max} (mixture of isomers) 3070, 1780, 1740, 1670, 1630, 1600 cm^{-1}. ^{1}H NMR (due to α-angelica lactone) δ 2.1 (3H, m), 3.3 (2H,m), 5.2 (1H,m). (due to β-angelica lactone) δ 1.5 (3H,d), 5.2) (1H,m), 6.2 (1H,dd), 7.6(1H,dd).

Reaction of α- Angelica Lactone (95) with Ethoxycarbonyl methylene - triphenylphosphorane (29).

Angelica lactone (two isomers) (100mg) and phosphorane (29), (350mg) were dissolved in dueterochloroform in an NMR tube. No reaction was observed at room temperature while at higher temperatures α- angelica lactone isomerised to β-angelica lactone with no further reaction.

Treatment of Phthalide (98) with Ethoxycarbonylmethylene triphenylphosphorane (29).

Phthalide (78), (134mg) and phosphorane (29), (350mg) were dissolved in deuterochloroform in an NMR tube. No reaction was observed after the solution had been heated at 90° for 6 hours.

Preparation of Benzofuran-2(3H)-one (100)

O - Hydroxyphenylacetic acid, prepared by the method of Levine, Eble and Fischbach[65], m.p. 148° - 149°, was distilled to give benzofuran-2(3H)-one one, b.p. 120° - 122°/13mm (lit[66] 245° - 249°).

Ethyl 2' - Benzofurylacetate.

A solution of ethoxycarbonylmethylene - triphenylphosphorane (29), (260mg) and benzofuran-2(3H)-one (100), (100mg) in deuterochloroform (0.5ml) was maintained at 50° for 48 hours. The intermediate (103) could not be detected by ^1H NMR during this period. Preparative TLC (ether/light petroleum, 3:1) gave ethyl 2' - benzofurylacetate (100mg, 72%) b.p, 120°/1mm (heated block) (lit[67] 163° - 165°/17mm).

ν_{max} 1740, 1610, 1590 cm^{-1}. ^1H NMR δ 1.3 (3H, t, $OCH_2\underline{CH}_3$), 3.8 (2H,s, CH_2), 4.2(2H, q, $O\underline{CH}_2CH_3$), 6.6 (1H, s, H3'), 7.1 - 7.6 (4H, m, aromatic H).

Preparation of d_1 - Ethoxycarbonylmethylene - triphenyl phosphorane (88).

Ethoxycarbonylmethylene - triphenylphosphonium bromide (4.3g) was dissolved in D_2O (10ml) and the solution stirred at room temperature for 30 minutes. Sodium hydroxide (1g) was then added and the solution stirred for a further 10 minutes. The precipitate was then filtered, dried, and recrystallised from ethyl acetate to give d_1 - ethoxycarbonylmethylene - triphenylphosphorane (88), (2.9g, 82%), 84% d_1, by ^1H NMR, m.p. 115° - 117°.

CHAPTER 2

(-) 2 - Carboxy - N - (1'-oxo-3'- phenylpropyl)- pyrrolidine (117).

This preparation was adapted from the method of Stoll[85]. 3 - Phenylpropanoyl chloride (16.8g, 0.1mmol) was added dropwise with stirring to a solution of L (-) - proline (5.7g, 50mmol) in 1N sodium hydroxide solution (50ml) at 0°. Sufficient 2N sodium hydroxide was added at the same time to keep the solution alkaline to phenolphthalein. Stirring was continued for a further hour at 0° and the solution then carefully acidified to Congo red with 2N hydrochloric acid. After stirring for a further 30 minutes, the precipitate was filtered off and washed with ice water. Recrystallisation from chloroform/light petroleum afforded 10.5g (85%) of the acid (117), m.p. 106° - 108°. (Found: C, 67.8; H, 7.1; N, 5.7% $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%). $[\alpha]_D$ (chloroform) =59°. ν_{max} 1720, 1580 cm^{-1}. ^1H NMR δ 2.0 (4H, m, $[H3]_2$, $[H4]_2$), 2.67, 2.93 (each 2H, m, $[H2']_2$, $[H3']_2$), 3.4 (2H, m, $[H5]_2$), 4.53 (1H, m, H2), 7.23 (5H, br s, aromatic H), 10.1 (1H, br s, $-CO_2H$).

(-) 2 - Azidocarbonyl - N - (1' - oxo - 3' - phenylpropyl) - pyrrolidine (118).

A stirred solution of the acid (117), (740mg, 3mmol) in dry tetrahydrofuran (15ml) at -20° under nitrogen, was treated successively with triethylamine (1.46ml, 3.3mmol) then ethyl chloroformate (0.32ml, 3.3mmol) and the solution was allowed to stir at -20° for 90 minutes. A solution of

sodium azide (215mg, 3.3mmol) in water (1ml) was then added and the solution stirred at -20° for a further 30 minutes. The reaction mixture was allowed to warm to room temperature and water (10ml) was added. The solution was extracted with dichloromethane (3 x 20ml), the combined extracts were dried and the solvent was removed at room temperature to give the azide (118), (740mg, 91%) as a colourless oil which was not further purified.

ν_{max} (THF solution) 2100, 1730, 1655 cm^{-1}.

(-) 2 - Isocyanato - N - (1'- oxo - 3'- phenylpropyl)- pyrrolidine (115).

Freshly prepared acyl azide (118), (740mg) in dry tetrahydrofuran (15ml) was heated under reflux for 90 minutes. After this time the infrared spectrum showed complete decomposition of the azide (118) to the isocyanate (115).

ν_{max} (THF solution) 2220, 1655 cm^{-1}.

2-Methyl - N - [1' - (1"-oxo-3"- phenylpropyl) pyrrolidin - 2' - yl] butanamide (114). (Dihydroodorine).

To a solution of freshly prepared isocyanate (115), (660mg, 2.7mmol) in dry tetrahydrofuran (15ml) at -78° under nitrogen, were added dropwise 1.2 equivalents of 2 - butylmagnesium bromide in ether. The solution was stirred for 2 hours at -78° and then allowed to warm to room temperature and stirring continued for 16 hours. Water (25ml) was then added at 0° and the solution extracted with

dichloromethane (3 x 40ml). The combined extracts were dried (potassium carbonate) and concentrated. Preparative TLC (ethyl acetate) afforded dihydroodorine (114) as a mixture of two diastereoisomers which were recrystallised from chloroform/light petroleum to give a solid (590mg, 72%), m.p. 107^{o} - 115^{o}. Repeated fractional recrystallisation (toluene/light petroleum) eventually gave a pure sample of epidihydroodorine, m.p. 125^{o} - 127^{o}. (Found: C, 71.5; H, 8.6; N, 9.1% $C_{18}H_{26}N_2O_2$ requires C, 71.5; H,8.7; N, 9.3%). ν_{max} 3260, 1660, 1640, 1530 cm^{-1}. ^{1}H NMR δ 0.82 (3H, t, $\underline{J}$ =7Hz, $[H4]_3$), 1.07 (3H, d, $\underline{J}$ =7Hz, C2-Me), 2.6, 2.82 (each 2H, m, $[H3"]_2$), 3.45 (2H, m, $[H5']_2$), 5.70 (1H, m, H2'), 6.5 (1H, m, NH), 7.27 (5H, br s, aromatic H).

Pure samples of both dihydroodorine and epidihydroodorine were eventually obtained by the use of high pressure liquid chromatography. The separation was carried out using two 500mm x 10mm columns in series, packed with 10μ Lichrosorb SI60. (Solvent: hexane / dichloromethane / isopropanol, 48:48:4). By the use of this system 1-2mg of the diastereoisomer mixture could be loaded per run, and the fractions obtained from this initial separation were reprocessed until pure. By this means pure samples of epidihydroodorine, m.p. 125^{o} - 127^{o}, $[\alpha]_D$ = $+35^{o}$ (ethanol) and dihydroodorine, m.p. 112^{o} - 114^{o}, (lit[69,70] 110^{o} - 112^{o}, 105^{o} - 106^{o}), $[\alpha]_D$ = $+8^{o}$ (ethanol) with spectral properties identical to an authentic sample of dihydroodorine, were obtained. (Found: C, 71.6: H, 8.7: N, 9.3% $C_{18}H_{26}N_2O_2$ requires C, 71.5; H, 8.7; N, 9.3%).

Hydrogenation of Odorine (104).

Odorine (104), (20mg) in ethanol (10ml) was hydrogenated at atmospheric pressure over platinum oxide (10mg). The catalyst was filtered off and the solvent removed to give a solid which was recrystallised from chloroform / light petroleum to give dihydroodorine (114), (18mg, 90%). m.p. 110° - 112° (lit[69,70] 110° - 112°, 105° - 106°). ν_{max} 3260, 1660, 1640, 1530 cm^{-1}. ^{1}H NMR δ 0.80 (3H, t, $\underline{J}$ =7Hz, $[H4]_3$), 1.07 (3H, d, $\underline{J}$ =7Hz, C2 -Me), 2.6, 2.82 (each 2H, m, $[H2"]_2$, $[H3"]_2$), 3.45 (2H, m, $[H5']_2$), 5.70 (1H, m, $[H2']_2$), 6.5 (1H, m, NH), 7.27 (5H, br s, aromatic H).

(-) 2 - Azidocarbonyl - N - (1'- oxo - 3'- phenylprop - 2' - enyl)pyrrolidine (119).

A solution of the acid (110), (490mg, 2mmol) in dry tetrahydrofuran (15ml) at -20° under nitrogen was treated with triethylamine (0.3ml, 2.2mmol) followed by ethyl chloroformate (0.21ml, 2.2mmol) and the mixture allowed to stir at - 20° for 90 minutes. A solution of sodium azide (143mg, 2.2mmol) in water (1ml) was then added and the solution stirred at -20° for a further 30 minutes. The reaction mixture was allowed to warm to room temperature and water (10ml) added. The solution was extracted with dichloromethane (3 x 20ml) and the combined extracts dried and the solvent removed at room temperature to give the azide (119), (470 mg, 87%) as a colourless oil.

ν_{max} (THF solution) 2160, 1739, 1648 cm^{-1}.

(-) 2 - Isocyanato - N - (1' - oxo - 3' - phenylprop - 2' - enyl)pyrrolidine (111).

Freshly prepared acyl azide (119), (470mg) in dry tetrahydrofuran (15ml) was heated under reflux for 60 minutes, after which time the infrared spectrum showed complete decomposition of the azide to the isocyanate (111). ν_{max} (THF solution) 2260, 1660 cm^{-1}.

2 - Methyl - N - [1' - (1" - oxo - 3" - phenylprop - 2" - enyl)pyrrolidin - 2' - yl]butanamide (104), (Odorine).

To a solution of freshly prepared isocyanate (111), (420mg, 1.73mmol) in dry tetrahydrofuran (15ml) at -78^{o} under nitrogen, were added dropwise 1.2 equivalents of 2 - butylmagnesium bromide in ether. The solution was stirred for 2 hours at -78^{o} and then for a further 14 hours at room temperature. Water (25ml) was then added at 0^{o} and the solution extracted with dichloromethane (3 x 40ml). The combined extracts were dried and concentrated. Preparative TLC (ethyl acetate) afforded odorine (300mg, 58%) as a mixture of two diastereoisomers. High pressure liquid chromatography (using conditions identical to those employed for the separation of the isomers of dihydroodorine) afforded pure samples of epiodorine, which crystallised from chloroform / light petroleum, m.p. 178^{o} - 180^{o}, (lit[70] 171^{o} - 172^{o}) (Found: C, 71.7; H, 7.9; N, 9.1% $C_{18}H_{24}N_2O_2$ requires C, 72.0; H, 8.1; N, 9.3%) $[\alpha]_D$ =

-2^{o} (ethanol). ν_{max} 3220, 1670, 1645, 1595, 1530 cm^{-1}. ^{1}H NMR δ 0.92 (3H, t, $\underline{J}$ =7Hz, $[H4]_3$), 1.08 (3H, d, $\underline{J}$ =7Hz, C2 - Me), 1.58 (2H, m, $[H3]_2$), 2.0 (5H, m, $[H3']_2$, $[H4']_2$, H2), 3.6 (2H, m, $[H5']_2$), 6.2 (2H, m, H2', NH), 7.02 (1H, d, $\underline{J}$ =16Hz, H2"), 7.3 - 7.7 (5H, m, aromatic H), 7.77 (1H, d, $\underline{J}$ =16Hz, H3"), ^{13}C NMR δ 12.0, 17.4, 21.7, 27.3, 34.6, 43.1, 46.2, 62.7, 118.2, 128.3, 128.8, 129.9, 134.9, 142.9, 165.9, 175.7, and odorine (104), identical to an authentic sample, which crystallised from chloroform / light petroleum m.p. 209^{o} - 211^{o} (lit[69,70] 218^{o} - 219^{o}, 205^{o}), ν_{max} 3220, 1670, 1650, 1600, 1540 cm^{-1}. ^{1}H NMR δ 0.78 (3H, t, $\underline{J}$ =7Hz, $[H4]_3$), 1.20 (3H,d, $\underline{J}$ =7Hz, C2 - Me), 1.55 (2H, m, $[H3]_2$), 2.0 (5H, m, $[H3']_2$, $[H4']_2$, H2), 3.5 (2H, m, $[H5']_2$), 6.2 (2H, m, H2', NH), 7.03 (1H, d, $\underline{J}$ = 16Hz, H2"), 7.3 - 7.7 (5H, m, aromatic H), 7.78 (1H, d, $\underline{J}$ = 16Hz, H3"). ^{13}C NMR δ 11.9, 17.6, 21.6, 27.0, 34.5, 43.1, 46.2, 62.8, 118.2, 128.3, 128.8, 129.9, 134.9, 143.0, 165.8, 175.8.

Hydrogenation of synthetic Odorine (104).

Odorine (20mg) in ethanol (10ml) was hydrogenated at atmospheric pressure over platinum oxide (10mg). The catalyst was filtered off and the solvent removed to give dihydroodorine (114) which was recrystallised from chloroform / light petroleum, (17mg, 85%), m.p. 111^{o} - 112^{o}, $[\alpha]_D$ (ethanol) = -9^{o}. Spectral data was identical to that of an authentic sample of dihydroodorine.

Hydrolysis of Dihydroodorine (114).

Synthetic dihydroodorine (114), (100mg) was heated under reflux in a 1:1 mixture of tetrahydrofuran and dilute hydrochloric acid (10ml) for 14 hours. The solution was then extracted with dichloromethane (2 x 20ml) and the combined organic phases extracted with 10% sodium hydroxide solution (3 x 20ml). The sodium hydroxide extracts were neutralised with dilute hydrochloric acid and extracted with dichloromethane (3 x 40ml). The combined organic extracts were dried and the solvent removed by distillation. The residue was taken up in chloroform (1.0ml) and the optical rotation of the mixture of 3 - phenylpropanoic and 2 - methylbutanoic acids measured.

Found : $[\alpha]_D = -5^o$.

Hydrolysis of Epidihydroodorine.

The hydrolysis of epidihydroodorine under conditions identical to those used for dihydroodorine afforded a mixture of acids with $[\alpha]_D = +7^o$ (lit[84] for S(+) 2 - methylbutanoic acid = -19.6^o).

Racemisation of (-) 2 - Carboxy - N - (1'- oxo - 3'-phenylprop - 2'-enyl)pyrrolidine (110).

A stirred solution of the acid (110), (100mg, 0.4mmol) in dry tetrahydrofuran (10ml) at -20^o was treated with triethylamine (0.06ml, 0.44mmol) followed by ethyl

chloroformate (0.04ml, 0.44mmol) and the solution allowed to stir at -20° for 90 minutes. A solution of sodium hydroxide (18mg, 0.44mmol) in water (0.5ml) was then added and the solution stirred at -20° for a further 30 minutes. The reaction mixture was allowed to warm to room temperature and water (10ml) added. The solution was extracted with dichloromethane (3 x 10ml), the combined extracts dried and the solvent removed under reduced pressure. The residue was recrystallised from chloroform / light petroleum to give 92mg (92%) of the acid (110), m.p. 106° - 108°. $[\alpha]_D$ = -136° (ethanol) (c.f. -212° for the starting acid). As a control experiment, the acid (110), (100mg) was dissolved in 10% sodium hydroxide solution (10ml) and allowed to stir at room temperature for one hour. The solution was acidified with dilute hydrochloric acid and extracted with dichloromethane (2 x 20ml). The organic extracts were dried and the solvent removed under reduced pressure. The residue was recrystallised from chloroform / light petroleum to give the acid (110), with $[\alpha]_D$ = -209°.

CHAPTER 3

Isolation of Scoparenonediol (128a)

The finely ground leaves and terminal branchlets of Eremophila scoparia (2,000g) were extracted with ether to yield an oil (78g, 4%). The crude extract was chromatographed on silica gel, using increasing percentages of ether in benzene, and a polar fraction (22g) containing the desired compounds collected. This fraction was again chromatographed on silica gel, eluting with mixtures of ether and benzene. It was noticed at this stage that a large amount of the acetate (133) had hydrolysed to the diol (128a) and that some of the diol had epimerised to the isomer (137). Further chromatography on silica gel, eluting with mixtures of ethyl acetate and light petroleum, afforded pure samples of scoparenonediol (128a) (2g), m.p. 125.5° - 126.5° (ethyl acetate), (Found: C, 71.3; H, 9.5 $C_{15}H_{24}O_3$ requires C, 71.4; H, 9.6%). ν_{max} 3300, 1660, 1620 cm^{-1}, λ_{max} 243 nm., ε = 15,300, ^1H NMR δ 0.9 (3H, s,) $[H14]_3$), 1.3(6H,s,$[H12]_3$, $[H13]_3$), 1.9 (3H, d, $\underline{J}$ = 2Hz, $[H15]_3$), 2.2 (2H,s,$[H1]_2$), 4.6(1H, dt, $\underline{J}$ = 5Hz, $\underline{J}$ = 10Hz, H8), 4.8(2H, br exch. -OH), 5.9(1H, br, H3) ^{13}C NMR δ 17.6 (q), 21.9, 24.0, 24.8, 29.7 (q), 38.3(s), 47.0(d), 48.4(t), 53.8 (2C,s), 67.7(d), 74.3(s), 126.6(d), 162.6(s), 198.9(s). m/e 252, 59(100%). $[\alpha]_D$ = +85.5° (chloroform).

Scoparenonediol isomer (137) (1.3g), m.p. 154° - 155° (Found: $(M+1)^+$ at m/e 253.180. $C_{15}H_{25}O_3$ requires $(M+1)^+$ at m/e 253.180). ν_{max} 3200, 1660, 1620 cm^{-1}, ^1H NMR δ 1.2(3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$),

2.1 (3H, d, $\underline{J}$ = 2Hz, $[H15]_3$), 2.3 (2H, s, $[H1]_2$), 4.1 (1H, dt, $\underline{J}$ = 5Hz, $\underline{J}$ = 10Hz, H8), 4.6 (2H, br, -OH), 6.0 (1H, br, H3). ^{13}C NMR δ 22.2, 23.7, 24.7, 27.4, 29.6, 37.3, 41.3, 45.4, 49.4, 51.8, 69.1, 74.5, 128.4, 161.5, 200.2.

Scoparenonediol acetate (133) (500mg), m.p. 131.5° - 133.5° (ethyl acetate), (Found: C,69.7; H,9.0 $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.9%), m/e 254 (M^+), 176 (100%), ν_{max} 3400, 1720, 1660, 1620 cm^{-1}. ^1H NMR δ 1.0(3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$), 2.0 (3H, d, $\underline{J}$ = 2Hz, $[H15]_3$), 2.1 (3H, s, $COCH_3$), 2.2 (2H, s, $[H1]_2$), 5.2(1H, dt, $\underline{J}$ = 5Hz, $\underline{J}$ = 10Hz, H8), 5.9(1H, br, H3).

Acetylation of Scoparenonediol (128a)

Scoparenonediol (128a) (150mg, 0.6mmol) and acetic anhydride (200mg, 2.0mmol) were dissolved in dry pyridine (2ml) and the mixture allowed to stand at room temperature for two days. The solution was diluted with water (20ml) and extracted with ether (3x20ml). The combined ether extracts were washed with dilute hydrochloric acid (2x20ml) and water (20ml), dried and the solvent removed under reduced pressure. Preparative TLC (ethyl acetate/ethanol, 12:1) afforded scoparenonediol acetate (133) (142mg, 78%), identical to a sample of the natural occurring acetate.

Dihydroscoparenonediol (142)

A solution of scoparenonediol (128a) (1g) in ethanol (25ml) was hydrogenated over platinum oxide (100mg). The

catalyst was filtered off (celite) and the solvent removed under reduced pressure. Recrystallisation from chloroform/light petroleum afforded dihydroscoparenonediol (142) (870mg, 87%), m.p. 156° - 157°. (Found: C, 70.7; H, 10.2, $C_{15}H_{26}O_3$ requires C, 70.8; H, 10.3%), ν_{max} 3400, 1700cm^{-1}. ^{1}H NMR δ 0.9 (3H, d, $\underline{J}$ =7Hz, $[H15]_3$), 0.95 (3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$), 2.25 (2H, s, $[H1]_2$), 4.0 (1H, dt, $\underline{J}$ = 5Hz, $\underline{J}$ = 10Hz, H8), 4.2 (2H, br, -OH).

Dihydroscoparenonediol Tosylate (143)

Dihydroscoparenonediol (142) (300mg, 1.18mmol) and p - toluenesulphonyl chloride (400mg, 2.1mmol) were dissolved in cold dry pyridine (3ml) and allowed to stand at 0° for two days. Water (0.5ml) was added and the mixture allowed to stand for 10 minutes. Water (25ml) was then added and the solution extracted with ether (2x20ml). The combined ether extracts were washed with dilute hydrochloric acid (2x20ml), water (20ml), dried, and the solvent removed under reduced pressure. Recrystallisation from light petroleum afforded the p-toluenesulphonate ester (143), (420mg, 87%), m.p. 110° - 112° (Found: C, 64.6; H, 8.2. $C_{22}H_{32}O_5S$ requires C, 64.7; H, 7.9%). ν_{max} 3400, 1700, 1360, 1170 cm^{-1}, ^{1}H NMR δ 0.9 (3H, d, $\underline{J}$ = 7Hz, $[H15]_3$), 0.95 (3H, s, $[H14]_3$), 1.3 (6H, s, [H12)]3, $[H13]_3$), 2.15 (2H, s $[H1]_2$), 2.45 (3H, s, Ar-Me), 5.0 (1H, dt, $\underline{J}$ = 5Hz, $\underline{J}$ = 10Hz, H8), 7.45, 7.9 (each 2H, each d, $\underline{J}$ = 8Hz, aromatic H).

Dihydropterocarpol (139)[114]

Pterocarpol (138) (40mg) in ethanol (10ml) was hydrogenated in the presence of 5% palladised charcoal (20mg). The catalyst was filtered off and the solvent removed under reduced pressure. Recrystallisation from ethyl acetate / light petroleum afforded dihydropterocarpol (139) (37mg, 92%), m.p. 120° - 122° (lit[114] 120° - 121°), ^{1}H NMR δ0.92 (3H, d, J = 8Hz, $[H15]_3$), 0.95 (3H, s, $[H14]_3$), 1.2 (6H, s, $[H12]_3$, $[H13]_3$), 4.0 (1H, m, H2).

Dihydropterocarpone (140)[114]

Dihydropterocarpol (139) (37mg) in pyridine, was added to excess Collins reagent and allowed to stand at room temperature for 16 hours. The solution was then diluted with water and extracted with ether. The ether extract was washed with dilute hydrochloric acid, dried, and the solvent removed to give a viscous liquid (25mg) which was not further purified. ν_{max} 3480, 1710 cm^{-1}. ^{1}H NMR δ 0.92 (3H, d, J = 7Hz, $[H15]_3$), 0.93 (3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$), 2.25 (2H, s, $[H1]_2$).

Epidihydropterocarpol (141)[114]

Dihydropterocarpone (140) (25mg) was reduced to epidihydro pterocarpol (141) by treatment with excess lithium aluminium hydride in dry ether for 30 minutes at room temperature. The excess lithium aluminium hydride was destroyed by the

addition of saturated ammonium chloride solution and the solution then extracted with ether, dried, and the solvent removed under reduced pressure. Preparative TLC (ether / light petroleum, 1:1) afforded epidihydropterocarpol (141) (18mg), m.p. 117° - 119°. ν_{max} 3400 cm^{-1}, ^{1}H NMR δ 0.87 (3H, d, J = 7Hz, $[H15]_3$), 0.9 (3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$), 4.2 (1H, m, H2). $[\alpha]_D$ = + 19° (chloroform).

2 - Carboethoxycyclohexanol (145)

Sodium borohydride (16mg, 5mmol) was added to a cooled solution of 2 - carboethoxy - cyclohexanone (144) (1.7g, 10mmol) in methanol (25ml). The solution was stirred for 30 minutes, acidified with dilute sulphuric acid, diluted with water (70ml) and extracted with ether (3x50ml). The combined ether extracts were washed with water (100ml), dried and solvent removed under reduced pressure. Distillation afforded 1.3g (76%) of a mixture of cis and trans 2 - carboethoxy - cyclohexanols (145), b.p. 120° - 130°/19mm (lit[117] 100° - 108°/8mm). ν_{max} 3510, 1740cm^{-1}. ^{1}H NMR δ1.3 (3H, t, J = 7Hz, $OCH_2\underline{CH_3}$), 3.2 (1H, br, OH), 3.9 (1H, br m, C<u>H</u>OH), 4.2 (2H, q, J = 7Hz, $OC\underline{H_2}CH_3$).

2 - Carbomethoxy - cyclohexanol (145a)[118]

Methyl salicylate (20g) in methanol (50ml) was hydrogenated over Raney nickel (2g) at 150°/1200 psi for 18 hours. The catalyst was filtered off and the solvent

removed. The residual oil was distilled (b.p. 110° - 130°/19mm) to give a mixture of cis and trans 2 - carbo - methoxycyclohexanols (145a) (17.4g, 87%) containing some methyl salicylate which could not easily be separated.

2 - (2' - Hydroxyisopropyl) - cyclohexanol (147) and (148)

A solution of the product mixture from the hydrogenation of methyl salicylate (10g, 63mmol) in dry ether (50ml) was added dropwise to methylmagnesium iodide (approximately 300mmol) in ether (100ml), and the solution heated under reflux for 14 hours. The reaction mixture was then poured onto crushed ice and acidified. The solution was extracted with ether (2x100ml) and the combined ether extracts washed with sodium bicarbonate solution and water. The organic layer was then dried and the solvent removed under reduced pressure. Chromatography on silica gel, eluting with mixtures of chloroform and light petroleum, afforded trans 2- (2' - hydroxyisopropyl) cyclohexanol (148) (3.1g, 29%), m.p. 76° - 79° (chloroform/light petroleum), (lit[119] 77° - 79°), ν_{max} 3350 cm^{-1}, ^1H NMR δ 1.2 (6H, s, $[H1']_3$, $[H3']_3$), 3.7 (1H, m, -CHOH), 4.5 (2H, s, OH), and cis 2 - (2'-hydroxyisopropyl) cyclohexanol (147), (4.4g, 41%) as a colourless oil, ν_{max} 3320 cm^{-1}, ^1H NMR δ 1.25, 1.4 (each 3H, s, $[H1']_3$, $[H3']_3$), 3.4 (2H, s, OH), 4.45 (1H, m, -CHOH).

Trans 2 - (2'-Hydroxyisopropyl) cyclohexyl p - Toluene - sulphonate (149)

trans 2 - (2'-Hydroxyisopropyl) - cyclohexanol (148) (500mg, 3.2mmol) and p - toluenesulphonyl chloride (900mg, 4.9mmol) were dissolved in cold dry pyridine (5ml) and allowed to stand at room temperature for 2 days. Water (0.5ml) was added and the solution allowed to stand for 10 minutes. Water (50ml) was then added and the solution extracted with ether (2x50ml). The combined ether extracts were washed with dilute hydrochloric acid (2x50ml), water (50ml) and dried. The solvent was removed and the product recrystallised from light petroleum to give the p - toluenesulphonate ester (149) (810mg, 82%), m.p. 87^{o} - 89^{o}, ν_{max} 3240, 1360, 1160 cm^{-1}, ^{1}H NMR δ 1.18, 1.23 (each 3H, s, $[H1']_3$, $[H3']_3$), 2.5 (3H, s, Ar-Me), 4.9 (1H, m, -CHO-), 7.4, 7.9 (each 2H, d, J = 8Hz, aromatic H).

Reduction of trans 2 - (2'-Hydroxyisopropyl) cyclohexyl p-Toluenesulphonate (149) with Lithium Aluminium Hydride.

A solution of the p - toluenesulphonate ester (149) (178mg, 0.57mmol) in dry ether (5ml) was added dropwise to a stirred solution of lithium aluminium hydride (40mg, 1.08mmol) in ether (10ml) and the solution heated under reflux for 16 hours. Excess hydride was decomposed by the dropwise addition of water and the solution then poured into cold dilute sulphuric acid. The mixture was then extracted with ether (2x30ml) and the combined ether extracts washed

with sodium bicarbonate solution, water, and dried. Preparative TLC (ether/light petroleum, 1:1) afforded 1 - (2' - hydroxyisopropyl) cyclohexene (150) (62mg, 77%), b.p. 100°/13mm (heated block), (lit[120] 33°/ 0.03mm), ν_{max} 3350, 1640cm^{-1}, m/e 140 (M+), 59 (100%), ^{1}H NMR δ1.2 (6H, s, $[H1']_3$, $[H3']_3$), 5.8 (1H, br s, H2).

Reduction of the p - Toluenesulphonate Ester (149) with Sodium Borohydride in Dimethylsulphoxide [121]

A solution of the p - toluenesulphonate ester (149) (100mg, 0.32mmol) and sodium borohydride (20mg, 0.7mmol) in dimethylsulphoxide (5ml) was stirred at 85° for 14 hours. Water (1ml) was then added dropwise and the solution stirred for a further 30 minutes, poured into water (20ml) and extracted with ether (3x15ml) . The combined ether extracts were washed with water (2x20ml) and dried. Preparative TLC (ether/light petroleum, 1:1) afforded 1 - (2'- hydroxy - isopropyl) - cyclohexene (150) (32mg, 71%) as the only major product.

Reduction of the p - Toluenesulphonate Ester (149) with a Copper Complex[122].

The copper complex was prepared as described by Masamune[122]. To an ice cooled flask containing cuprous iodide (124mg, 0.64mmol) and tetrahydrofuran (1ml) under nitrogen, was added dropwise with stirring a 1M solution of lithium trimethoxyaluminium hydride (1.3ml) and sufficient tetrahydrofuran to facilitate stirring (total approximately

4ml). After the addition was completed, the resulting brown mixture was stirred for 30 minutes at 0° and then the p - toluenesulphonate ester (149) (100mg, 0.32mmol) in tetrahydrofuran (1ml) was added all at once. After 15 minutes the cooling bath was removed and the mixture stirred at room temperature for 18 hours. Methanol (1ml) was slowly added and the solution diluted with ether (20ml) and filtered through celite. The solution was then washed with saturated ammonium chloride solution, dried, and the solvent removed. ^{1}H NMR showed the recovered material to be a mixture of the p - toluenesulphonate ester (149) (60%) and 1 - (2' - hydroxyisopropyl) - cyclohexene (150) (40%).

Reduction of the p - Toluenesulphonate ester (149) with Aluminium Hydride[123].

The p - toluenesulphonate ester (149) (100mg, 0.32mmol) in tetrahydrofuran (1ml) was added to a solution of lithium aluminium hydride (29mg, 0.75mmol) and aluminium chloride (34mg, 0.25mmol) in dry tetrahydrofuran (5ml) under nitrogen and the solution stirred at room temperature for 18 hours. Excess hydride was destroyed by the dropwise addition of a saturated ammonium chloride solution and the solution then diluted with water (10ml), extracted with ether (2x10ml), dried, and the solvent removed. The ^{1}H NMR spectrum of the residue showed an olefinic product.

Reduction of Dihydroscoparenonediol p - Toluenesulphonate (143) with Lithium Aluminium Hydride.

1. The p - toluenesulphonate ester (143) (175mg, 0.43mmol) in dry tetrahydrofuran (5ml) was added dropwise to a stirred solution of lithium aluminium hydride (40mg, 1.08mmol) in tetrahydrofuran (10ml) and the solution then heated under reflux for 16 hours. Excess hydride was decomposed by the dropwise addition of water and the mixture then poured into cold dilute sulphuric acid and extracted with ether (3x20ml). The combined ether extracts were washed with sodium bicarbonate solution and water, dried and the solvent removed under reduced pressure. Preparative TLC (ether) afforded the elimination product (151) (66mg, 63%) m.p. 108° - 125° (chloroform / light petroleum) contaminated with another olefinic product from which it could not be separated. (Found M^+ at m/e 238.193 $C_{15}H_{26}O_2$ requires M^+ at m/e 238.193). ν_{max} 3340, 1605 cm^{-1}. ^1H NMR δ 1.25 (6H, s, $[H12]_3$, $[H13]_3$), 4.25(1H, m, H2), 5.55 (1H, br, H8).

2. The p - toluenesulphonate ester (143) (150mg) was reduced with lithium aluminium hydride, as above, except that the reaction was carried out at -78°. Preparative TLC (ether) afforded two products : the elimination product (151) (37mg, 41%), again contaminated with another olefinic product, and the triol (152) (40mg, 45%) m.p. 160° - 162° (chloroform/light petroleum) ν_{max} 3280 cm^{-1}, ^1H NMR δ 1.1 - 1.4 (methyl groups, complex), 2.6 (3H, br, OH), 3.6

- 4.3 (2H, m, H2, H8), m/e 239(M^+ - OH), 241(M^+ - CH_3).

Hydrogenation of the Elimination Product (151).

The olefin (151) (40mg) in ether (5ml) was hydrogenated over platinum oxide (10mg). The catalyst was filtered off and the solvent removed under reduced pressure. Preparative TLC (ether) afforded epidihydropterocarpol (141) (15mg) m.p. 117° - 118° (chloroform/light petroluem), (Found M^+ at m/e 240.209. $C_{15}H_{28}O_2$ requires M^+ at m/e 240.209) ν_{max} 3450 cm^{-1} ^1H NMR δ0.87 (3H, d, $\underline{J}$ = 7Hz, $[H15]_3$), 0.9 (3H, s, $[H14]_3$), 1.3 (6H, s, $[H12]_3$, $[H13]_3$), 4.2 (1H, m, H2). $[\alpha]_D$ = +19.5° (chloroform).

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